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MARCH 1952
VOLUME 67 NUMBER 3

Published Monthly by
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

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A. M. A.
Archives of Neurology and Psychiatry

VOLUME 67 MARCH 1952 NUMBER 3

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TUMORS OF THE MEDULLA OBLONGATA

IRVING S. COOPER, M.D.
JAMES W. KERNOHAN, M.D.
AND
WINCHELL McK. CRAIG, M.D.
ROCHESTER, MINN.

THE FIRST report of a tumor in the medulla oblongata was that of Chevalier [1] in 1834. Since that initial report there have appeared in the medical literature descriptions of a total of 57 cases of primary tumors of the medulla. Practically all these reports have described single cases or have mentioned the tumors in question incidentally in treatises on other subjects. Only two detailed studies of neoplasms confined to the medulla have been published. The first of these was the report by Sokoloff [2] in 1887, who reported a glioma of the medulla oblongata in a 5-year-old boy. He collected seven cases of medullary glioma from the world literature. Chabrol,[3] in 1908, was stimulated by an instance of sarcoma of the medulla oblongata, which he had recently observed, to review the subject of tumors of the medulla and to report 90 cases of various types of space-occupying lesions affecting this section of the brain stem. However, the original reports on which Chabrol's review was based disclose the fact that in only 21 of these 90 cases were the lesions primary intramedullary tumors of the bulb, the others being either extramedullary neoplasms or non-neoplastic processes. In a report of tumors of the brain stem in 1934, Hare and Wolf [4] included three cases in which the tumor was confined to the medulla oblongata or involved that region principally. Foerster and Gagel,[5] in 1939, described 12 cases of astrocytoma of the brain stem, in 4 of which the medulla was the site of greatest neoplastic involvement. Many of the individual reports of cases, particularly those of Osler [6] (1888), Graham [7] (1896), and Glynn [8] and of two

Fellow in Neurosurgery, Mayo Foundation (Dr. Cooper).

From the Section on Pathologic Anatomy (Dr. Kernohan) and the Section on Neurologic Surgery (Dr. Craig), the Mayo Clinic.

1. Chevalier, T. W.: Case of Tumor in the Medulla Oblongata, London M. Gaz. **14**:10-15 (April) 1834.

2. Sokoloff, N.: Zwei Fälle von Gliom des centralen Nervensystems, Deutsches Arch. klin. Med. **41**:443-471 (Dec.) 1887.

3. Chabrol, E.: Les tumeurs du bulbe, Encéphale **1**:403-437 (May) 1908.

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5. Foerster, O., and Gagel, O.: Die Astrocytome der Oblongata, Brücke und des Mittelhirns, Ztschr. ges. Neurol. u. Psychiat. **166**:497-528, 1939.

6. Osler, W.: Glioma of the Medulla Oblongata, J. Nerv. & Ment. Dis. **15**:172-176 (March) 1888.

(Footnotes continued on next page)

cases from the Massachusetts General Hospital,[9] have afforded excellent detailed studies of single lesions. However, there has not been, up to this time, a clinicopathologic study of any appreciable number of tumors confined to the medulla. Our purpose, therefore, is to describe the signs, symptoms, and pathologic features in 15 histologically verified tumors of the medulla oblongata.

NATURE OF THE STUDY

This series includes only cases of histologically verified tumors which were confined to the medulla oblongata or in which extension of the tumor cephalad into the pons or caudad into the spinal cord was minimal as compared with neoplastic involvement of the medulla itself. Metastatic malignant processes and invasive tumors arising outside the medulla were not included. In 14 of these cases the lesions were verified at necropsy; in 1 case confirmation was made surgically. The tumors were grouped histologically according to the classification of Bailey and Cushing,[10] as well as by the classification recently suggested by one of us (Kernohan). Since the report by Russell and Bland,[11] which demonstrated the relation of spongioblastoma polare to the astrocytomas, we have listed these tumors in the astrocytoma group.

INCIDENCE

The average age of the 15 patients in this series was 26.2 years, the range being from 26 months to 58 years (Table 1). Five patients, or 33.3%, were in the first decade of life, and of these, four were less than 5 years old. There were no patients between the ages of 10 and 20 years, and only three in the third decade of life. There were three patients in the fourth decade, two in the fifth, and one in the sixth. Thus, it would seem, on the basis of our series, that children in the first 10 years of life are affected considerably more frequently by neoplasms of the medulla oblongata than are persons of any other age group. Persons in the seventh and eighth decades of life are not represented in this series. This incidence according to the age of the patient parallels closely that of a series of pontine tumors studied by Turner.[12] The three patients who had tumors of the medulla oblongata in the series of Hare and Wolf all were less than 8 years old. Alpers and Yaskin [13] stated that most pontine gliomas occur in children, and although it is apparent that tumors

7. Graham, J. E.: A Tumor of the Medulla Oblongata, Canad. Pract. **21**:549-558 (Aug.) 1896.

8. Glynn, T. R.: Tumour of the Medulla Oblongata in the Neighbourhood of the Calamus Scriptorius, Liverpool M.-Chir. J. **7**:428-433 (April) 1887.

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11. Russell, D. S., and Bland, J. O. W.: Further Notes on the Tissue Culture of Gliomas with Special Reference to Bailey's Spongioblastoma, J. Path. & Bact. **39**:375-380 (Sept.) 1934.

12. Turner, T. R.: Tumors of the Pons; a Clinicopathological Study of 30 Histologically Verified Cases, Thesis, Mayo Foundation, 1944.

13. Alpers, B. J., and Yaskin, J. C.: Gliomas of Pons: Clinical and Pathologic Characteristics, Arch. Neurol. & Psychiat. **41**:435-459 (March) 1939.

of the medulla also affect the very young, they do not occur so often in children as do pontine gliomas. Six of the patients in our series were females and 9 were males.

SYMPTOMS

No typical clinical syndrome was presented by these patients with tumors of the medulla oblongata. Although the medulla contains five pairs of cranial nerves, which if involved provide signs and symptoms that are particularly helpful in the localization of lesions to this structure, the involvement of these nerves was not so frequent as might be expected. Moreover, signs of involvement of cranial nerves, when they were present, tended to appear late in the course of the patient's illness. Tumor of the medulla oblongata is a disease of protean clinical manifestations.

Ataxia.—The most constant symptom was ataxia, which appeared at some time during the course of the disease in 10 patients. Ataxia was also the most frequent

TABLE 1.—*Incidence of Lesion According to Age and Sex, and Duration of Symptoms Prior to Admission of Patients*

Case No.	Age (Yr.)	Sex	Duration of Symptoms Prior to Admission (Mo.)
1	3	F	5
2	39	M	20
3	32	F	7
4	4½	M	1½
5	58	M	1
6	44	M	10
7	5	F	8
8	26 mo.	M	4
9	9	F	6
10	49	M	26
11	29	F	24
12	4	M	2½
13	24	F	8
14	38	M	12
15	29	M	24
Average	26.2	6 F 9 M	10.6

early symptom in eight patients; that is, it was one of the first three symptoms to appear in 52% of the patients and was present at some time during the course of the disease in 67%. Ataxia was the initial symptom in one patient. The frequency of occurrence of ataxia is due to involvement of the spinocerebellar tracts and of the gracile and cuneate nuclei.

Peripheral Weakness.—Weakness of one or more extremities was the next commonest symptom, appearing in nine, or 59%, of the patients. In view of the prominence of the pyramidal tracts in the internal structure of the medulla oblongata, more frequent motor weakness might be expected. This relative infrequency of involvement of the pyramidal tracts is due to the tendency of these neoplasms to be located in the upper two-thirds of the medulla, thereby involving the corticospinal pathways by means of pressure rather than direct invasion. Turner [12] noted involvement of the pyramidal tracts in 66% of cases of pontine tumors. The greater frequency of occurrence of this symptom in pontine tumors is undoubtedly due to the more diffuse and widespread location of fibers of the pyramidal tracts in the pons than in the medulla.

Headache.—Headache was the third commonest symptom, being present in eight patients, in five of whom it was one of the three earliest symptoms to appear. In three of these five patients headache was the initial symptom. The headaches were occipital or cervico-occipital in six patients. One patient complained of headache localized to the vertex of the head, and in one the headache was supraorbital. Five of the eight patients complaining of headache experienced one or more signs of increased intracranial pressure.

Diplopia.—The next commonest symptom in the series was diplopia or, in children, internal strabismus of one eye, as observed by the parents. Diplopia was present in seven patients, or in 46%. Internal strabismus and diplopia resulted from frequent involvement of the abducens nerve. In several cases this involvement occurred as a result of direct pressure, by the enlarged medulla, on the abducens nerve as it courses between the pons and the medulla after emerging from the former. Moreover, because of its long intracranial course, the abducens nerve is the cranial nerve most frequently affected by increased intracranial pressure. In one case the intrapontine portion of the abducens nerve was involved by invasion of the tumor directly into the pons, although the neoplasm was located primarily in the medulla. Therefore, in tumors of the medulla oblongata paralysis of the external rectus muscles is seldom of precise localizing value.

Vomiting.—Seven patients suffered from vomiting, in three of whom it was projectile in character. Vomiting was an early symptom in four of these patients and was the initial symptom in one. In at least three of these patients there was no sign of increased intracranial pressure, and it is likely that the vomiting was due to involvement of the dorsal motor nucleus of the vagus nerve.

Numbness and Paresthesia.—Subjective numbness and paresthesia were present in only six patients. In three sensory symptoms appeared early, but the symptoms did not initially herald the onset of the disease in any of the patients.

Hiccup.—Hiccup was a persistent and distressing symptom in five patients and in two it was one of the three earliest symptoms. Three patients had persistent hiccup in the absence of any sign of increased intracranial pressure.

Vertigo and Dysarthria.—Vertigo and dysarthria each was present in five patients. In three patients dysarthria was due to involvement of the hypoglossal nerve; in one it was probably due to involvement of suprasegmental fibers to the hypoglossal nucleus, and in one the speech disorder was of the cerebellar type.

It is seen in this survey of the nine commonest symptoms that none, with the possible exception of dysarthria, can be regarded as of specific localizing value. Headache was localized to the occipital or cervico-occipital area in 75% of the patients in whom it was present. Diplopia, ataxia, peripheral muscular weakness, vomiting, hiccup, and vertigo, although suggesting the medulla oblongata as a possible site of localization, cannot be regarded as pathognomonic of a lesion in this structure.

Other Symptoms.—Because of their unusual interest, it would seem worth while to mention some of the less frequent symptoms.

Three patients showed personality changes. These mental symptoms were apparently due to secondary cerebral changes. Intention tremor, blurred vision, and coma each was present in three patients. All other symptoms were present in only two

patients or less. Of the symptoms which appeared in only two cases, the most interesting were epileptiform convulsions. It is not clear whether these seizures were due to (1) secondary edema or a vascular lesion of the cerebrum, (2) afferent stimulation of the subthalamus and cortex from injury zones in the ascending sensory tracts, thereby initiating convulsive activity, or (3) efferent motor impulses, arising from damaged zones in the pyramidal tracts and acting as trigger areas, similar to those shown by Kugelberg [14] to occur in injured peripheral nerve pathways. Convulsions were reported in 5 of the 57 cases of medullary tumors in the literature.[15]

Tinnitus was present in two patients, in one of whom unilateral nerve deafness was demonstrable. Noyes and Dana [15b] and Gray [16] reported tinnitus in individual cases of bulbar neoplasms.

SIGNS

Cranial Nerves.—Signs referable to the cranial nerves were noted in seven, or 46%, of the patients in this series, and when present they tended to be multiple. Two patients had involvement of the oculomotor nerve, as evidenced by absence of pupillary reaction both to light and in accommodation. This sign was bilateral in one patient and unilateral in the other. One patient had weakness of the temporal and masseter muscles unilaterally, suggesting involvement of the trigeminal nerve. Pathologic study did not reveal any neoplastic invasion of the pons or midbrain in patients exhibiting signs referable to the oculomotor or trigeminal nerve. Six patients presented signs of involvement of the sixth cranial nerve, as evidenced by internal strabismus or varying degrees of weakness of the external rectus muscle.

The facial nerve was the most frequently affected cranial nerve, signs of facial weakness being present in all seven patients in whom signs of involvement of cranial nerves were noted. Signs of injury to the glossopharyngeal and vagus nerves were noted four times. The hypoglossal nerve was involved three times, and the spinal accessory nerve twice.

Pyramidal and Extrapyramidal Signs.—Signs of involvement of the pyramidal tract and of areas outside the pyramidal tract, that is, muscular weakness, the Babinski reflex, or increased deep reflexes, were the most frequently encountered neurologic abnormalities. They occurred in 12 of the 15 patients. In nine patients these signs occurred bilaterally.

Ataxia and Nystagmus.—Ataxia was noted in nine patients and often was so severe as to interfere with locomotion. Nystagmus was present in eight and incoordination of the upper extremities in six patients. These "cerebellar" signs were

14. Kugelberg, E.: "Injury Activity" and "Trigger Zones" in Human Nerves, Brain **69**:310-324 (Dec.) 1946.

15. (*a*) Kjelberg, cited by Chabrol.[3] (*b*) Noyes, H. D., and Dana, C. L.: Tumor of the Medulla and Left Anophthalmus, Boston M. & S. J. **122**:304 (March 27) 1890. (*c*) Newman, F.: Case of Sarcoma of the Medulla, Projecting into the Fourth Ventricle, Intercolon. M. J. Australia, Melbourne **8**:631 (Dec.) 1903. (*d*) von Slotow, G.: Diffuses Gliom der Medulla oblongata im Kindesalter, Monatsschr. Psychiat. u. Neurol. **23**:445-446, 1908. (*e*) Brunel, M.: Sur une variété de tumeurs du tronc cérébral: des tumeurs intra-bulbaires, Gaz. méd. France **45**:395-396 (April 1) 1938.

16. Gray, A. A.: A Case of Tumour of the Medulla and Pons Causing Deafness and Other Remarkable Symptoms, Tr. Internat. Otol. Cong. **6**:378-384, 1900.

frequently present simultaneously and in several instances led to a clinical diagnosis of cerebellar tumor, particularly in children.

Impairment of Somatic Sensory Perception.—Impairment of somatic sensory perception (pain, touch, temperature) occurred in four patients, and one presented unilateral hyperesthesia. The latter occurrence is not readily explained in a case in which the pathologic process was confined to the medulla oblongata. Although a secondary vascular thrombosis was not noted on pathologic study, such a lesion may have been present in the thalamus to account for this perversion of touch and pain perception.

Intracranial Pressure.—Signs of increased intracranial pressure were present in six patients, in all of whom papilledema was observed. These findings are summarized in Table 2.

Astereognosis.—Astereognosis was noted in one patient. Astereognosis was regarded by Nielsen and co-worker [17] as impairment of the faculty of recognition of the shape and texture of objects in the absence of any impairment in light-touch perception. It is regarded as a specific tactile agnosia and is thought to result from a lesion of the parietal lobe. Roussy and Lévy [18] reported a case of glioma of the

TABLE 2.—*Signs of Increased Intracranial Pressure in Six Cases of Primary Tumor of the Medulla Oblongata*

Sign	Number of Times Noted	Per Cent
Papilledema	6	39
X-ray evidence (enlarged sella turcica, digital markings, etc.)	5	32.6
Electroencephalogram	2	13
Macewen's sign	1	7
Tense, bulging fontanel	1	7

medulla in which the presence of astereognosis had resulted in a mistaken diagnosis of a lesion of the parietal lobe, in consequence of which surgical exploration of the parietal region was performed, with negative results. It is likely that in our case, as well as in that of Roussy and Lévy, astereognosis was due to impairment of fibers mediating position sensation, which traverse the medulla. Consequently, the concept of astereognosis as a specific type of agnosia pathognomonic of a lesion of the parietal lobe must be regarded with caution when this finding is evaluated clinically.

Glycosuria.—The presence of glycosuria in patients with bulbar tumors has been mentioned frequently by earlier authors.[19] Only one of our patients had glycosuria; this patient had a hemangioendothelioma of the medulla oblongata associated with cystic disease of the pancreas.

Clinical Syndromes.—It is possible to distinguish no less than six distinct clinical syndromes presented by these 15 patients. First, signs due to involvement of cranial

17. Nielsen, J. M., and FitzGibbon, J. P.: Agnosia, Apraxia, Aphasia: Their Value in Cerebral Localization, Los Angeles, Los Angeles Neurological Society, 1936.

18. Roussy, G., and Lévy, G.: Existence d'une dissociation, dite corticale, des troubles de la sensibilité, par atteinte bulbo-protubérantielle et médullaire supérieure, Rev. neurol. **1**:145-162 (Feb.) 1930.

19. de Jonge, D.: Tumor der Medulla oblongata: Diabetes mellitus, Arch. Psychiat. **13**:658-670, 1882. Bensusan, A.: Notes on a Case of Glycosuria Caused by Tumour of the Medulla, Transvaal M. J. **4**:182, 1908-1909.

nerves, pyramidal tracts, and cerebellar tracts; second, signs referable to cranial nerves and pyramidal tracts without cerebellar signs; third, cerebellar signs and symptoms alone; fourth, signs referable to the pyramidal and somatic sensory tracts alone; fifth, an objectively normal nervous system, with no neurologic signs; sixth, syncopal and convulsive types, with episodes of syncope and convulsions as the chief characteristics.

REPORT OF CASES

Six illustrative cases are presented briefly. Physical findings not herein referred to may be presumed to have been normal.

CASE 2.—A miner aged 39 was first seen at this clinic complaining of occipital headache of four months' duration. Twenty months prior to admission he had noted the sudden onset of diplopia, and in the ensuing period, prior to his admission, he had been troubled by hoarseness, slurred speech, fatigability, and several episodes of a projectile type of vomiting.

Significant results of neurologic examination were horizontal nystagmus on gaze to the right or left; paralysis of the left external rectus muscle, and paresis of the entire left side of the face, the left vocal cords, and the left side of the tongue. In addition, there were hemiparesis on the right, with increased deep reflexes, and pronounced ataxia of all extremities. A roentgenogram of the skull revealed enlargement of the sella turcica, suggestive of increased intracranial pressure.

Suboccipital craniotomy was performed; the medulla oblongata was seen to be diffusely enlarged, as though by an infiltrating neoplasm. The patient died suddenly on the seventh postoperative day.

Necropsy revealed the medulla to be uniformly enlarged and to measure 4 by 2.6 cm. On cross section the medulla appeared congested. A smooth, gray-white tumor appeared to fill the entire medulla, extending into the upper part of the cervical portion of the spinal cord and into both restiform bodies. Microscopic examination revealed the neoplasm to be an astrocytoma, Grade 1, composed almost entirely of bipolar spongioblasts.

This patient exhibited symptoms and neurologic signs referable to the pyramidal and "cerebellar" systems, as well as signs of involvement of multiple cranial nerves.

CASE 5.—A farmer aged 58 was seen at the clinic in August, 1930. Five weeks prior to his admission, the patient noted the sudden onset of diplopia and right internal strabismus. Simultaneously, headache, localized to the vertex of the head, began to occur daily. Two weeks prior to the patient's admission he had noticed weakness of the right arm and leg, which progressed to complete paralysis of these extremities. Ten days prior to his admission, dysphagia had developed rapidly, and feeding by tube became necessary.

Neurologic examination revealed nystagmus of the left eye on medial or lateral gaze. The right external rectus muscle was completely paralyzed, and there was moderate weakness of the muscles of the left side of the face and of the right half of the tongue. There was no voluntary motion of the left extremities, and sensory perception for all modalities was absent in these extremities. Twelve hours after his admission, the patient died suddenly in acute respiratory failure.

Necropsy revealed diffuse enlargement of the right half of the medulla oblongata, extending from the caudal border of the pons Varolii to the upper region of the cervical part of the spinal cord. On cross section, this section of the cord appeared reddish and necrotic. Microscopic examination revealed a fibrillary astrocytoma, Grade 1, diffusely infiltrating the upper two-thirds of the medulla oblongata.

In this case, the patient's entire illness lasted only five weeks, and three cranial nerves, the pyramidal tract, and the medial lemniscus were involved, without cerebellar signs or symptoms. The low grade of malignancy of this neoplasm, from the standpoint of microscopic characteristics, was not in keeping with the rapidly fatal course of the patient's illness.

Case 6.—A farmer aged 44 was admitted to the clinic complaining of cervico-occipital headache, of 10 months' duration, and of recurrent hiccup and vertigo, of 3 months' duration. Results of the neurologic examination were without significance except for stiffness of the neck and minimal nystagmus. Ventriculograms demonstrated complete block at the level of the fourth ventricle. Cerebrospinal fluid obtained during tapping of the ventricles contained 4,000 mg. of protein per 100 cc.

Suboccipital craniotomy was performed; the medulla oblongata was seen to be the site of a large cyst, the contents of which were evacuated. A reddish granular tumor was then seen extending from the floor of the fourth ventricle into the substance of the medulla oblongata, enlarging it in a fusiform manner. The patient died eight hours after operation.

In addition to the tumor seen at operation, which occupied the upper two-thirds of the medulla, there was a syringomyelic cavity of the lower part of the medulla and the upper part of the cervical region of the spinal cord, as well as a small tumor nodule, 5 by 7 mm., in the right hemisphere of the cerebellum. The neoplasm of the medulla, as well as that of the cerebellum, was a typical hemangioendothelioma. A hemangioendothelioma of the medulla is pictured in Figure 1.

This case exemplifies a tumor of the medulla oblongata which produced no demonstrable neurologic signs.

Case 7.—A girl aged 5 years was observed by her parents to stagger when walking. She tired easily and complained of difficulty in voiding. Several months after the onset of the

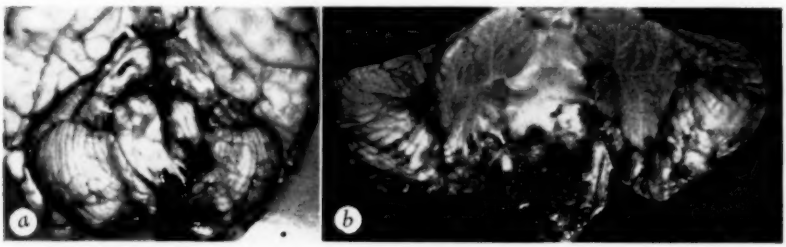

Fig. 1.—(*a*) Marked enlargement and discoloration of medulla oblongata produced by hemangioendothelioma; (*b*) longitudinal section of medulla oblongata, showing invasion of the bulb by this tumor.

staggering gait, the patient complained of pain in both eyes. At this time, she was observed to have bilateral internal strabismus, which disappeared after two weeks. Dysphagia, weakness of the left extremities, and cervico-occipital pain had developed, and the patient was admitted to this clinic eight months after the onset of symptoms.

The only sign of involvement of a cranial nerve was failure of the pupils to react to light or in accommodation. There was hemiparesis on the left, with increased deep reflexes and Babinski and Chaddock responses on the same side. Roentgenograms of the head revealed secondary pressure erosion of the sella turcica. The patient became stuporous and died in acute respiratory failure three days after admission.

Postmortem examination revealed the medulla oblongata to be enlarged to twice its normal size by a white, firm neoplasm which occupied the upper two-thirds of the structure and blocked the fourth ventricle. Microscopic examination revealed the tumor to be a fibrillary astrocytoma, Grade 1.

In this case, neurologic signs referable almost solely to the pyramidal and sensory tracts were exhibited. The clinical picture was very similar to that of the demyelinating encephalitides.

Case 9.—A white girl aged 9 years awoke one morning with a severe headache and within a few moments was screaming with pain and seemed irrational. This episode lasted six hours

and was relieved after the patient vomited. There were no more symptoms for one month, after which time the child had daily, early-morning occipital headaches, sharp and knife-like in character. On two occasions her left forearm and hand became numb and weak, this sensation lasting from three to five minutes each time.

She was seen at the clinic six months after the initial episode, at which time neurologic examination revealed no observations referable to the cranial nerves, pyramidal tract, or somatic sensory faculties. Significant results of neurologic examination were bilateral impairment of the finger-to-nose and heel-to-knee tests, ataxia, hyporeflexia in both lower extremities, cervical rigidity, and minimal nystagmus on lateral gaze. Bilateral papilledema measured 4 D. on the left and 3 D. on the right. The perimetric visual fields revealed an enlarged blind spot bilaterally. A roentgenogram of the head revealed extensive destruction of the sella turcica secondary to increased intracranial pressure. The clinical impression was that of a neoplasm of the posterior cranial fossa, probably cerebellar.

Surgical exploration revealed a large tumor originating in the medulla oblongata, which was enlarged to twice normal size. The neoplasm was seen to be growing around the medulla and the caudal end of the pons, displacing the left cerebellar lobe laterally. The part of the tumor which was not intrinsic in the medulla oblongata was removed. The patient died suddenly on the fifth postoperative day, after a bout of acute dyspnea.

Microscopically, the tumor was ependymoma, Grade 2, of very cellular nature, simulating an astrocytoma. In some areas of the lesion, however, there was a typically epithelial type of ependymal-cell formation; oligodendrocytes also were noted.

This case is an instance of a tumor of the medulla oblongata in which there were no signs or symptoms due to involvement of the cranial nerves or pyramidal tract. All the symptoms appeared clinically to be due to increased intracranial pressure, and the neurologic signs were limited to those of the "cerebellar" type.

Case 10.—A man aged 49 was first seen at the clinic in February, 1940. At that time, his complaints were general malaise, lassitude, anorexia, and fatigability, of 16 months' duration For one year he had been subject to episodes of lightheadedness and blackness before his eyes when rising to a standing position. For the same period he had been troubled by hiccup occurring daily, after meals, and lasting 30 to 60 minutes. For six months prior to his initial visit to the clinic the patient had noted a feeling of "lifelessness" in his left extremities. Although sensory perception was normal, these extremities felt "dead." The patient's wife said that for the preceding two years the patient had been depressed and uninterested in his surroundings. She noticed that he had staggered on one or two occasions while walking. Results of neurologic examination, general physical examination, and laboratory examinations, including a roentgenogram of the head, had been normal at the first visit.

The patient was next seen 10 months after his initial visit. He complained at this time of choking on solid foods during the preceding eight months. For five months prior to this visit he had been subject to sudden episodes of extreme weakness, which caused him to fall to the floor but during which there was no impairment of consciousness. In October, 1940, convulsions had begun to occur; originally, they were tonic, consisting of loss of consciousness with extreme opisthotonos and tonic extension of the extremities, and lasting about 10 minutes. During the week previous to his admission, however, the patient had had several generalized convulsions with both tonic and clonic elements, the clonic element usually being confined to, or starting in, the left upper extremity. The patient also complained of occipital headaches and weakness of the left extremities. He stated that the most distressing symptom was paroxysmal coughing, occurring particularly at mealtime.

Neurologic examination revealed bilateral nystagmus on lateral gaze in either direction. There was questionable weakness of the left side of the palate and the left side of the tongue. Sensory perception was intact, except for impaired position and vibration sensation in the left lower extremity. Ability to perform the finger-to-nose and heel-to-knee tests was minimally impaired on the left. There was no papilledema. Roentgenograms of the head disclosed no abnormality. Examination also revealed extreme postural hypotension. Two days after admission the patient had a generalized convulsion and died in acute respiratory distress.

Postmortem examination revealed marked enlargement of the medulla oblongata by an infiltrating neoplasm, which formed a protrusion, 3.5 cm. in its greatest dimension, on the left lateral surface of the medulla. The greater portion of the neoplasm was confined to the left superior aspect of the medulla, but it also extended across the midline to involve the right half of the bulb. The tumor extended from the inferior aspect of the roof of the fourth ventricle to the level of the pyramidal decussation. Microscopically, the neoplasm proved to be a glioblastoma multiforme (astrocytoma, Grade 3). This neoplasm is pictured in Figures 2 and 3.

This case illustrates many of the diagnostic pitfalls which may be encountered in cases of neoplasms of the medulla oblongata. The neurologic consultants who examined this patient recorded several factors which militated against the possibility of a tumor of the posterior cranial fossa: (1) the length of illness, 26 months,

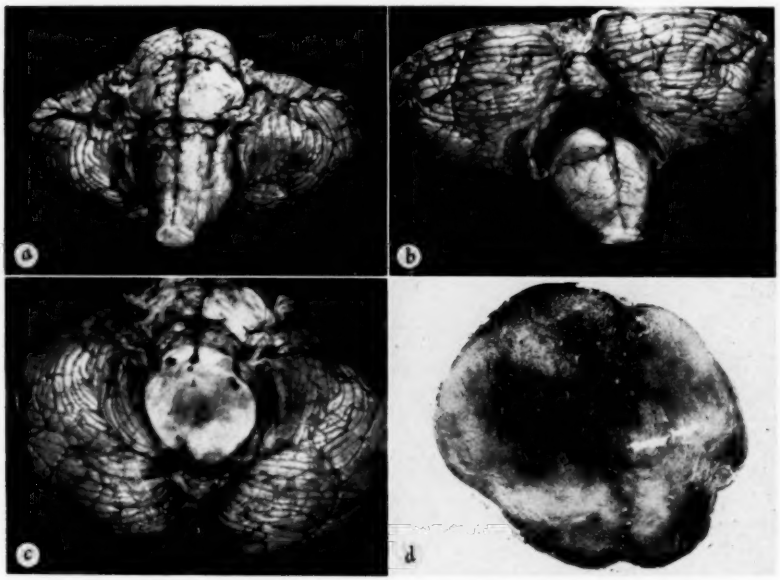

Fig. 2.—(*a*) Ventral view of medulla oblongata in Case 10, showing diffuse enlargement of upper two-thirds of bulb; (*b*) dorsal view of medulla in same case, showing diffuse manner of enlargement; (*c*) cross section of brain stem, demonstrating enlargement of bulb by infiltrating neoplasm and petechial hemorrhage; (*d*) cross section of bulb, 2½ times actual size, showing infiltrating character of tumor.

during most of which time the symptoms were vague and ill-defined; (2) absence of definite signs of involvement of the cranial nerves; (3) absence of signs of increased intracranial pressure, and (4) presence of epileptiform convulsions. The significance of the marked postural hypotension was also difficult to interpret.

PATHOLOGIC ASPECTS

In this series 11 of the neoplasms were gliomas: Seven were astrocytomas, Grade 1; 2 were glioblastoma multiforme (or astrocytomas, Grades 3 and 4); 1 was a very cellular ependymoma, and 1 was an oligodendroglioma. Four of the

Fig. 3.—(*a*) Section of neoplasm in Case 10, demonstrating pleomorphism, cellularity, and giant-cell formation of a glioblastoma multiforme (hematoxylin-eosin stain; × 125); (*b*) higher magnification of same section, allowing a closer view of tumor giant cell (hematoxylin-eosin stain; × 425); (*c*) Bodian-stained section of same tumor, demonstrating preservation of axis-cylinders of medulla oblongata in presence of a malignant invasive neoplasm. This preservation accounts for the relative preservation of neurologic function in the presence of an infiltrating glioma (× 500).

tumors were hemangioendotheliomas. Since the histologic characteristics of these neoplasms were the same as those of similar tumors situated in other parts of the brain, detailed gross and microscopic descriptions will not be given.

The duration of symptoms prior to admission of the patients who had hemangioendothelioma was 10.9 months, essentially the same as the average of 10.6 months for patients in the entire series and of 10 months for patients who had gliomas. The two patients who had a glioblastoma multiforme in this series had symptoms for 26 and 24 months, respectively, prior to their admission.

COMMENT

The most outstanding feature in the cases of tumor of the medulla oblongata reported in the literature, as well as in the cases in the present report, is the extreme variability of the symptoms and signs presented by individual patients. It seems somewhat paradoxical that tumors affecting this small segment of the brain stem should produce such widely varying clinical pictures. Cimbal [20] reported two cases of glioma of the medulla oblongata in which the gross and histopathologic pictures in the one were almost identical with those in the other. One of his patients had symptoms and signs referable to the cranial nerves, the spinocerebellar system, and the pyramidal tract, while the second patient died after an illness characterized only by lassitude, vomiting, and high fever.

Another incongruous feature of many of these cases is the tremendous size of the tumor revealed at necropsy, in contrast with the relative paucity of neurologic signs demonstrated. Hare and Wolf,[4] Schmidt,[21] and Newman [15c] commented on this aspect of the disease. Lhermitte and Guccione [22] demonstrated histologically that it is the persistence of axis-cylinders, by virtue of their relative resistance to pressure phenomena in the midst of an infiltrating glioma, that accounts for the comparative preservation of neurologic function in the presence of large neoplasms. The similar resistance of ganglion cells undoubtedly is responsible for the infrequency of occurrence of signs of involvement of cranial nerves. (Babonneix and Vincent,[23] Stevenson and Friedman,[24] Roussy and Lévy,[18] and many others pointed out the pitfalls encountered in the diagnosis of tumors of the medulla. Newmark and Lennon,[25] Starr,[26] and Oppenheim [27] reported cases in which medullary tumors simulated tumors of the cerebellum.) The lesion in our Case 9 was of this type.

20. Cimbal, W.: Beiträge zur Lehre von den Geschwülsten im 4. Ventrikel, Arch. path. Anat. **166**:289, 1901.

21. Schmidt, H. D.: A Case with Tumors in the Fourth Ventricle of the Brain, Unaccompanied by Special Nervous Symptoms, J. Nerv. & Ment. Dis. **9**:509-513 (July) 1882.

22. Lhermitte, J., and Guccione, A.: Persistance des cylindre-axes dans les tumeurs du système nerveux et leurs altérations, Compt. rend. Soc. de biol. **67**:190-192 (July) 1909.

23. Babonneix, L., and Vincent, C.: Tumeur bulbo-médullaire, Rev. neurol. **63**:702-705 (May) 1935.

24. Stevenson, L. D., and Friedman, E. D.: Tumours Involving the Ventral Aspect of the Pons and Medulla, Including 2 Chordomas, Brain **59**:291-301 (Oct.) 1936.

25. Newmark, L., and Lennon, M. B.: A Case of Tumor of the Medulla Oblongata, California J. Med. **8**:159-161 (May) 1910.

26. Starr, M. A.: Tumors of the Brain in Childhood: Their Variety and Situation, with Special Reference to Their Treatment by Surgical Interference, M. News **54**:29-37 (Feb.) 1889.

27. Oppenheim, cited by Newmark and Lennon.[25]

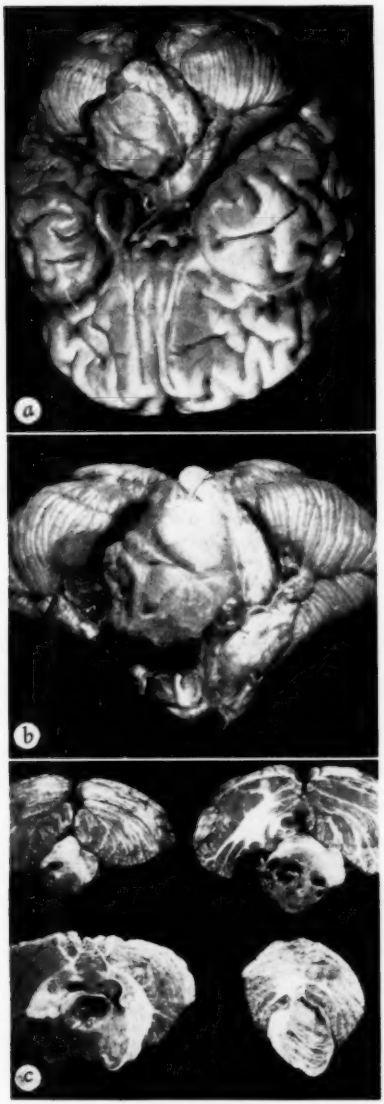

Fig. 4.—(*a*) Appearance of entire brain after sudden death caused by a large cystic astrocytoma of medulla oblongata; (*b*) close-up view of cystic mass completely disfiguring medulla; (*c*) cross sections of medulla, demonstrating cystic and neoplastic destruction of bulb.

The incongruity between the histologic picture and the duration of the disease has already been mentioned.

One other outstanding feature of these cases is the frequency of sudden, unexpected death from acute respiratory failure. Each patient with a neoplasm affecting the medulla oblongata is a potential victim of sudden death, as emphasized by this occurrence in the cases of Virchow [28] (1864) and Collins [29] (1897) and the frequency of sudden respiratory death in our own cases. A cystic astrocytoma which was asymptomatic until it resulted in sudden, unexpected death is pictured in Figure 4.

SUMMARY

The clinical signs and symptoms and the pathologic findings in 15 patients with primary tumor of the medulla oblongata are reported. The protean nature of the clinical manifestations of tumors of the medulla is emphasized. Of the 15 neoplasms, 7 were astrocytomas (Grade 1); 2, astrocytomas (Grades 3 and 4; glioblastomas multiforme); 1, an ependymoma (Grade 2); 1, an oligodendroglioma, and 4, hemangioendotheliomas. The most frequent symptoms of these patients were ataxia, muscular weakness, diplopia, headache (usually cervico-occipital), and vomiting. Diplopia, ataxia, and headache were the most frequent early symptoms. The neurologic signs most frequently encountered were those of the pyramidal and extrapyramidal tracts, ataxia, nystagmus, incoordination of the upper extremities, and signs of involvement of the cranial nerves. Nine of the 15 patients presented bilateral signs. Six had evidence of increased intracranial pressure.

The Mayo Clinic.

28. Virchow, R. L., cited by Chabrol.[3]

29. Collins, J.: Gliom der Medulla oblongata, Deutsche Ztschr. Nervenh. **10**:453-466 (July 8) 1897.

NEUROPSYCHIATRIC ASPECTS OF CUSHING'S SYNDROME

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SINCE Harvey Cushing's original description of a disease occurring in association with basophile adenoma of the pituitary gland,[1] it has become widely recognized that the characteristic clinical picture may occur not only in association with this specific anatomical lesion, but with a wider variety of pathological conditions.[2] Thus, it has become customary to speak of Cushing's syndrome rather than of Cushing's disease, and to apply the latter term, if at all, to those cases in which a basophile adenoma is demonstrable. Furthermore, it now seems clear that, whatever additional pathological changes are uncovered at autopsy, the clinical picture of both Cushing's disease and Cushing's syndrome can be regarded as the result of adrenocortical hyperfunction, whether neoplastic or hyperplastic in anatomical expression.

As this study, therefore, is concerned principally with neuropsychiatric aspects, which are in themselves of a primary clinical nature, only the term Cushing's syndrome will be used in reference to the cases described. However, mention will be made later of certain pathological conditions within the central nervous system which are of interest in their possible relation to some of the mental changes described, although whether these are of primary etiological importance or secondary to adrenal hyperfunction cannot as yet be positively determined.

It is not proposed to enter into any detailed description of the purely physical manifestations of this syndrome. Most of these are generally known and have been well described by Albright [2a] and other authors. Some of the physical changes, such as disfigurement, which may be striking and is produced by obesity, changes in the skin, hirsutism, and spinal deformity from osteoporosis, are worthy of further consideration, owing to their psychological implications. The same may be said of the muscular weakness and fatigability which commonly occur, and of impotence

Dr. Fuller Albright and Dr. Anne P. Forbes and their associates at the Massachusetts General Hospital allowed ready access to their case records and personal files.

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1. Cushing, H.: (*a*) Bull. Johns Hopkins Hosp. **50**:137, 1932; (*b*) Further Notes on Pituitary Basophilism, J. A. M. A. **99**:281 (July 23) 1932.

2. (*a*) Albright, F.: Harv. Lect. (1942-1943) **38**:123, 1943. (*b*) Albright, F., and MacMahon, H. E.: Bull. New England M. Center **3**:35, 1941. (*c*) Kepler, E. J., and Locke, W.: Textbook of Endocrinology, Editor, R. H. Williams, Philadelphia, W. B. Saunders Company, 1950, p. 180.

and loss of libido. In addition, there are alterations in the metabolism of sugar, protein, and electrolytes, some or all of which may be, and probably are at times, intimately concerned with mental abnormality.

Although Cushing's syndrome can be considered a relatively uncommon disorder, in view of the interest taken by some psychiatrists in the mental changes occurring in association with other forms of endocrine disorder, it is perhaps surprising that on the whole the condition should have received from them such scant attention. Writers on endocrinology have been more prolific. Soffer [3] gives some information, though he deals chiefly with the mental manifestations of the adrenogenital syndrome. Kepler and Locke,[2c] however, believe that severe mental disorder is more prevalent in patients having Cushing's syndrome than in those in whom symptoms of the adrenogenital syndrome predominate. Cushing himself mentioned the occurrence of mental symptoms in a number of the cases which he described, although he made no further reference to these disorders in his summary of the characteristics of the disease.[1a]

In addition, there have been from time to time descriptions of isolated cases of Cushing's syndrome occurring in association with psychosis or other severe mental disorder. Oldenberg [4] described one such case and referred to a number of others, including that of Maclay and Stokes.[5] The latter, in addition to the case they themselves described in detail, enumerated the chief abnormal mental findings in a number of other cases, details of which they obtained from the study of medical records. Lintz [6] described three cases, and, although many of his conclusions were of a somewhat speculative nature, he stated the belief that some psychiatric abnormality occurs in the majority of cases and, while occasionally severe and obvious, is mild in most cases, and therefore overlooked.

An estimate of the total incidence of mental disturbance was made by Jonas,[7] who in 1935 reported that this complication occurred in 20.5% of cases of Cushing's syndrome. More recently, Merritt,[8] in a conference talk at the Institute of Living, noted that psychotic manifestations developed in 7 of 34 cases, a figure which coincides closely with the previous estimate. There is, however, reason to believe that if minor mental changes be taken into account the over-all incidence is even higher.

In addition to, and apart from, cases with psychiatric complications, cases with pathological involvement of the central nervous system have been recorded, and the possible association of these findings with mental abnormality have been discussed. Schlezinger and Horwitz [9] described a patient with mental changes of a depressive nature and physical signs of extrapyramidal disease in whom autopsy revealed changes in the right frontal lobe. These lesions, in their opinion, suggested the possibility of an encephalitic-neuroendocrine disorder. Oldenberg [4] advanced the view that Cushing's syndrome may be a postencephalitic phenomenon or a sequel of encephalosis [sic] complicating pertussis or other acute infectious disease. Heinbecker's [10] discovery of atrophy of the paraventricular nuclei of the hypo-

3. Soffer, A.: Diseases of the Adrenals, Philadelphia, Lea & Febiger, 1946, p. 218.
4. Oldenberg, F.: Schweiz. Arch. Neurol. u. Psychiat. **59**:319, 1947.
5. Maclay, W. S., and Stokes, A. B.: J. Neurol., Neurosurg. & Psychiat. **1**:110, 1938.
6. Lintz, W.: M. Times, New York **69**:424, 1941.
7. Jonas, V.: Časop. lék. česk. **74**:1913, 1463, 1935.
8. Merritt, H. H.: Digest Neurol. & Psychiat., Inst. of Living **19**:108 (March) 1951.
9. Schlezinger, N. S., and Horwitz, W. A.: Am. J. Psychiat. **96**:1213, 1940.
10. Heinbecker, P.: Medicine **23**:225, 1944.

thalamus is of interest, but, in addition, in three of six cases of one series described by him [10] and in one of two other cases [11] some degree of internal hydrocephalus was present, and in some instances other pathological changes in the brain were noted. In only one of all his cases, however, did he refer to the occurrence of mental derangement.

Recent experiences with psychiatric illnesses, of both minor and major proportions occurring as a complication of therapy with corticotropin [11a] and cortisone, such as those that have been described by Clark, Bauer, and Cobb [12]; Hoefer and Glaser,[13] and Merritt,[8] have led to the not unreasonable belief that they may have a connection with the mental changes which have been observed in Cushing's syndrome. In addition, Merritt and others have pointed out that many of the physical side-effects observed during corticotropin and cortisone therapy are reminiscent of those resulting from the adrenocortical hyperfunction seen in Cushing's syndrome. On the surface, it would at least seem possible that the accidental production of mental symptoms by these therapeutic agents, in the first instance, may parallel the spontaneous and endogenous occurrence of similar phenomena, in the second. It is this matter, which will be discussed, that has primarily been responsible for arousing our interest in the subject.

The material on which this paper is based has been obtained from the study of a series of 25 patients with Cushing's syndrome, all of whom have been seen at the Massachusetts General Hospital during the last 16 years. There has been no selection of cases, and all cases in which the diagnosis was made and in which records were available have been considered. For convenient comparison, the basic relevant facts on all these cases are presented in tabulated form (Table 1).

One patient with severe mental symptoms (Case 1) has been followed extensively; one (Case 2) was seen after recovery, and five others (Cases 4, 6, 17, 24, and 25) were seen and studied during some stage of their illness or recovery. Further information concerning these and 18 other patients has been gleaned from a study of their medical records. Although these records are extensive as regards physical and biochemical findings, details of the psychiatric aspects tend to be somewhat scanty, except for the four patients who exhibited the greatest degree of mental disturbance and who have been studied more fully.

In three of the cases of less severe disturbance in which there was opportunity for personal assessment after perusal of the records, and in which a psychiatrically oriented inquiry was made, it became clear that the mental symptoms were somewhat more extensive than was at first apparent.[14]

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11. Heinbecker, P., and Pfeiffenberger, M.: Am. J. Med. **9**:3, 1950.

11a. Corticotropin is the generic term for the adrenocorticotropic hormone, often abbreviated to ACTH.

12. Clark, L.; Bauer, W., and Cobb, S.: New England J. Med., to be published.

13. Hoefer, P. F. A., and Glaser, G. H.: Effect of Pituitary Adrenocorticotropic Hormone (ACTH) Therapy: Electroencephalographic and Neuropsychiatric Changes in 15 Patients, J. A. M. A. **143**:620 (June 17) 1950; Proceedings of First Clinical ACTH Conference, Toronto, The Blakiston Company, 1950, p. 536.

14. Further information on five other patients in the series was obtained from a description of their personality and behavior by an observant head nurse who had been intimately concerned with their care and treatment while in the hospital. For four of these patients the same conclusion could be drawn as for the patients seen personally, namely, that the degree of disturbance was more than that evident from mere perusal of the records; in the fifth patient, in whose notes there was no record of mental symptoms, this apparent normality was confirmed.

Classification of the patients according to the degree of disturbance becomes, therefore, somewhat arbitrary. Few would disagree that at least three, and possibly four, of the patients could be classified as "psychotic"; however, this term will not be employed, as it is believed that all degrees of abnormality may be observed in this series. Instead, for comparative purposes, it has been found convenient to

TABLE 1.—*Clinical Data on Twenty-Five Cases of Cushing's Syndrome*

Case No.		Sex	Age	Approximate Length of History	Anatomical Diagnosis	Mental Symptoms*	Principal Treatment	Outcome
1	R. A.	F	25	8 mo.	Adrenal hyperplasia	++++	Operation	Recovery
2	M. C.	F	31	1 yr.	Adenoma of right adrenal	++++	Operation	Recovery
3	J. D.	F	37	18 mo.	Adenoma of left adrenal	++++	Operation	Recovery
4	M. A.	F	25	4 yr.	Adrenal hyperplasia	+++(+)	Operation; irradiation	Partial remission; now hypoadrenalism
5	B. An.	F	43	14 yr.	Adrenal hyperplasia; basophile adenoma	++	Irradiation	Partial remission; death of cerebral hemorrhage
6	D. O'B.	F	33	2-3 yr.	Adrenal hyperplasia	+(+)	Operation; irradiation	Current case; still hypertension
7	B. Ab.	F	33	5 yr.	Adenoma of right adrenal	++(+)	Operation	Death after operation
8	M. d'A.	F	25	7 yr.	Adenoma of right adrenal	+	Operation (gall bladder)	Death of congestive heart failure after operation
9	L. S.	M	30	2 yr.	Adrenal hyperplasia	+(+)	Operation	Partial remission; still mild symptoms
10	W. S.	M	27	4-5 yr.	Adrenal hyperplasia	+(+)?	Operation; irradiation	Not fully known (?); some hypoadrenalism
11	L. B.	F	37	3-4 yr.	Adrenal hyperplasia	+(+)	Operation; irradiation	Current case (?); further treatment needed
12	A. D.	F	30	1-2 yr.	Adrenal hyperplasia	(+)	Operation; irradiation	Postoperative death of pulmonary embolism
13	T. B.	F	51	2 yr.	Carcinoma, left adrenal	(+)	Nil	Death
14	R. B.	F	47	3-4 yr.	Adrenals reported to be normal size (??)	++	Irradiation; adrenal biopsies	Remission
15	C. de B.	M	31	3 yr.	Adrenal hyperplasia	+	Operation; irradiation	Recovery
16	M. M.	F	49	3-4 yr.	Adrenal hyperplasia	(+)	Operation (unilateral)	Recovery
17	S. W.	F	33	14 yr.	Adenoma, left adrenal	++	Operation; irradiation	Recovery
18	A. P.	F	56	15 mo.	Carcinoma, left adrenal	—	Operation	Death, postoperative, of cardiac failure
19	I. G.	F	11	3-4 yr.	Adrenal hyperplasia	—	Irradiation; adrenal biopsies	Recovery
20	M. S.	F	42	2 yr.	Adenoma, left adrenal	—	Operation	Recovery
21	R. B.	F	30	1 mo.	Adenoma, left adrenal	—	Operation	Recovery
22	B. V.	F	20	2 yr.	Adrenal hyperplasia	++	Irradiation; adrenal biopsies	Remission
23	M. Sn.	F	36	2 yr.	Carcinoma, left adrenal	+	Nil	Death due to secondary metastases
24	R. K.	F	32	1-3 yr.	Adenoma, left adrenal	++(+)	Operation	Recovery
25	S. B.	F	62	6 mo.?	Adrenal hyperplasia	++	Operation	Current case

* ++++ indicates severe mental symptoms; ++, moderate severity; + and +(+), mild mental symptoms; (+), mental symptoms very mild or insignificant. Parentheses indicate some doubt in assessing severity.

group the patients into five categories according to the severity of their mental symptoms. This placing is based on the quantity, type, and relative severity of symptoms recorded in the history of each particular patient, as well as on information gained from the other sources already mentioned. Using this approximation, we find that, in addition to the 4 severely disturbed patients, 6 of the remaining 21 patients are classifiable as moderately disturbed, and 8, as mildly disturbed, whereas 3 of the remaining 7 patients had relatively insignificant psychiatric symptoms. Four patients are thought to have been normal.

The case histories of the four most disturbed patients are presented in considerable detail, and, in somewhat less detail, are given the histories of two other, moderately disturbed, patients. Aside from the fact that rather more information about these two is available than for some of the other patients, both having been seen personally, they were chosen because they appeared to demonstrate two rather

TABLE 2.—*Psychiatric Abnormalities Noted in Less Severely Affected Patients**

Case No.	Symptoms	Results
5	Patient tired, depressed, cried easily; pressure headaches severe at times; condition noted as variable	Marital discord, ending in divorce at onset of illness; very long history; moderate mental symptoms
7	Nervousness; emotional instability; screaming and panting attacks; possible hysteria; abnormal drowsiness at times	Illness began with "nervous breakdown" following death of second child; moderately severe mental disturbance
8	Increased emotional lability and irritability; frontal headaches and fine tremor of hands	Mild relatively insignificant mental symptoms
9	Great variability in mood; increasing nervousness and depression; decreased libido and potency; dulling of emotional responses; attacks of palpitations; some headaches	Reacted badly to physical changes; mild to moderate mental disturbance
10	Intermittent headaches; patient described as "very neurotic"; threat to withdraw medication after operation produced nausea and vomiting; patient somewhat uncooperative	Information scanty; psychiatric component said to be hard to evaluate; probably mild to moderate mental symptoms
11	Very apprehensive; tended to minimize symptoms when question of operation was raised	Described as a "very abnormal woman"; information regarding mental symptoms rather scanty, however
12	Depression at times; complaint of loss of interest and desire in normal activities; occasional frontal headaches	Severe social and domestic problems; very little mental abnormality
13	Headaches and palpitations attributed initially to nervousness; apathy	Very little mental abnormality
14	Increasing nervousness and discouragement; ("feels like wreck!"); patient noted as less alert and more forgetful as illness continued	Very long history with 15 hospital admissions; moderate personality change
15	Weakness, lethargy, loss of libido, and lack of ambition; patient somewhat depressed at times	Mild relatively insignificant mental symptoms
16	Pressure headaches; palpitations; complaint of lack of "pep" for some time after operation	Insignificant mental symptoms
17	Dulness; patient somewhat discouraged and depressed; numbness and tingling; increasing pressure headaches; very complaining—aches and pains everywhere; irritability	Patient anxious about herself long after operation, though finally improved; moderate mental symptoms in part reactive to death of mother
22	Severe frontal headaches and dizzy spells; mood variable, cooperative at times, irritable at others; dulness and lack of response; intermittent nervous attacks; trouble with memory	Relatives described her personality as becoming much more alert as recovery occurred; moderate personality disturbance
23	Headaches and dizzy spells; trembling; patient slow, though cooperative	Mild relatively insignificant mental symptoms
25	Marked lethargy and drowsiness; irritability and depression at times; apprehensiveness at times; some crying spells; remarkable inactivity	Patient gives impression of rather low intelligence; probably moderate degree of mental disturbance

* Cases 6 and 24 are not included, as these have been more fully described. Cases 18, 19, 20, and 21 have no recorded psychiatric abnormalities.

different types of minor psychiatric disturbance which may be met with in association with this syndrome. The psychiatric symptoms of the remaining patients, together with relevant comments, are summarized and presented in tabulated form (Table 2).

Many of the available biochemical and metabolic data not considered completely relevant to this study are omitted, and the detailed description of the physical findings is reduced to a minimum. Further information concerning these and other aspects of some of the cases has been presented and discussed elsewhere.[2a,b]

REPORT OF CASES

CASE 1 (M. G. H. 279588).—Mrs. R. A., aged 25, an American-born housewife, white, was admitted to the hospital on Feb. 19, 1951.

Family History.—She was the second of four siblings, all girls, and there was no history of mental illness or significant physical disease in the family.

Previous History.—The patient was born a normal full-term infant, although with instrumental delivery. Development was normal, and there was no history of previous illness, except for uncomplicated measles, scarlet fever, and chickenpox during childhood.

She did well at school, was the co-editor of the school paper, and had had several poems published in local newspapers. No neurotic traits were described, and her premorbid personality seems to have been satisfactory, although she was stated to be somewhat quieter and more reserved than her sisters. She was apparently happily married and had one son, aged 3 years.

Present Illness.—The patient had been in good health until eight months before admission. In May, 1950, she started to become full in the face and to gain weight, especially around the shoulder girdle. She began to fear she had cancer and consulted a doctor, who reassured her on this point. During the next few months her complexion, which had previously been fair, became darker and more plethoric. Her eyebrows grew heavier and darker, and hair started to grow on her face. These changes, and an increase in weight, caused her some concern. Menstruation, which had been normal since onset, at the age of 13, became irregular and scanty, and during the next eight months she missed three periods altogether. In August, 1950, she was discovered to be hypertensive and about this time complained of muscular weakness and inability to stand for long. She began to brood, became unable to concentrate, was irritable toward her 3-year-old son and careless of his welfare, and had crying spells. Sexual intercourse, which had previously been pleasant and satisfactory, now became repulsive, and she felt that she could obtain satisfaction only by masturbation; furthermore, she seemed to fear that her sex was changing.

Examination.—Physical examination on admission was suggestive of a mild Cushing syndrome. She had a round, florid face, with some hair on her cheeks, an intrascapular "buffalo" pad of fat, and some obesity about her shoulders and neck. There were acne over the chest, bruising of the legs, and abdominal and gluteal striae, some having the characteristic purple coloration. There were generalized weakness of the trunk and extremities, and gross, evanescent tremors of the fingers and hands, though, except for this, examination of the central nervous system, revealed nothing of significance. The blood pressure was 150/100.

Laboratory studies revealed slight polycythemia (6,700,000 red blood cells per cubic millimeter), a low fasting eosinophile count (9 cells per cubic millimeter), and a mildly abnormal decreased sugar-tolerance curve. Serum sodium, potassium, chloride, and carbon dioxide were within normal limits, and the 17-ketosteroid-excretion levels varied from 23.4 to 28.2 mg. in 24 hours. A roentgenogram of the skull showed a normal sella turcica and no evidence of raised intracranial pressure. There was no osteoporosis of the vertebrae, though slight compression of the inferior margin of the fifth lumbar vertebra was present. An electroencephalogram was normal, and the electrocardiogram was also normal.

Mental State.—On admission she showed considerable agitation and depression, and during the next few days her condition underwent further deterioration. She became extremely depressed, with striking retardation at times and severe agitation at others. She had ideas of guilt and unworthiness and frequently expressed hypochondriacal delusions. She complained that she could hear her own thoughts spoken as though within her head and indicated that these thoughts were of an unpleasant and sexual nature. She searched through her past experience for happenings with which she might reproach herself and recounted these in a low, monotonous voice. She was quite without insight and refused to believe that she could be ill, stating that the voice within her head told her that this was not so.

Her mental condition worsened, and she began to express frankly homosexual ideas. She was uncooperative and at times refused food or to have laboratory investigations carried out, and on several occasions she asked that the police might be called, so that she might be taken to prison. She was strongly suicidal, and on several occasions she made attempts to strangle herself.

Operation and Progress.—On March 1, 1950, operative exploration, by Dr. Oliver Cope, revealed a hyperplastic left adrenal, and four-fifths of the gland was removed. There were no physical complications from this operation, but she became, if anything, even more depressed. She refused to admit that she had been operated on but complained that two men had come into her room and beaten her. She made two further attempts at suicide and on one occasion almost succeeded in hanging herself. She expressed strong ideas of reference, stating that her thoughts were being read and that ideas were being placed in her head. She continued to recount her supposed misdeeds in a low, monotonous voice and wrote, slowly, one or two lengthy confessions, which reproduced exactly the delusional content of her speech.

On March 13, 1950, a subtotal adrenalectomy was carried out on the opposite side, the condition of her right adrenal being similar to that on the left. She withstood this operation well, though there was a suggestion of adrenal deficiency, which responded adequately to therapy with cortisone, which drug was withdrawn after three days without ill-effect.

For eight or nine days after operation her mental condition remained qualitatively unchanged, but after this a slow and somewhat erratic improvement took place. First, she became less agitated, though retardation was still very apparent. Then her delusional ideas appeared to be losing their force. Three weeks after the second operation she was greatly improved, started to take an interest in her appearance, and on occasions became moderately sociable with other patients. Nevertheless, her behavior continued to be rather erratic; she would suddenly become much more depressed, irritable, and angry and would again express marked ideas of reference, all without apparent exciting cause. She also started to show interest in her son when he was brought in to visit her and expressed anxiety as to his welfare.

Concomitant with her mental improvement, her physical condition became more normal, her face losing some of its swollen appearance and dusky-red color. Her skin commenced peeling and she started to lose weight; she became more active, and there was less evidence of fatigue and muscular weakness.

By April 21, 1950, her condition had undergone a great change. Retardation had disappeared, and there was little evidence of her former depressed state in her behavior, her appearance, or the content of her speech. The variability in her condition, which had been previously observed, had also disappeared, and she was considered well enough to be discharged to the care of her parents.

Follow-Up Observation.—She has been seen only twice since discharge, at fortnightly intervals. On each occasion she was noted to have improved both physically and mentally. She is now no longer depressed and, except for slight emotional lability, can be considered mentally recovered.

CASE 2 (M. G. H. 718895).—Mrs. M. C., aged 31, an American-born housewife of Irish extraction, was admitted to the hospital on Nov. 1, 1950.

Family History.—The patient was one of six siblings, one of whom had died during an influenza epidemic. There was no history of mental illness or of significant physical disease in the family.

Previous History.—Her birth, development, and schooling had been normal; her previous personality was unremarkable, and she had been happily married for eight years, having three children, a girl aged 4 years and twins aged 2½ years. The only history of illness was that of an attack of arthritis in the knees at the age of 11 years, influenza at 12 years, and hay fever for three consecutive seasons some time before.

Present Illness.—One year before admission she began to show a gain in weight, which at first was controlled to a certain extent by diet and administration of thyroid. Three months later her abdomen began to enlarge, and at the same time she complained of generalized weakness, particularly in the legs, which gave way on occasions and caused her to fall to the floor.

After this, menstruation became scant, and for seven months prior to admission she had complete amenorrhea. Her weakness progressed, and she complained of foggy vision and a heavy feeling in the eyes and head, though not of actual headaches.

Seven months before admission, up to which time she had exhibited little or no mental abnormality, she suddenly became excited, hyperactive, apparently disoriented, and rambling in

speech and refused food and drink. She was admitted to a mental hospital and given 10 electroshock treatments, after which she became quieter, more detached, and apathetic and seemed "in a world of unreality," though oriented.

Three months after this, the possibility of Cushing's syndrome was entertained, and irradiation to the pituitary was commenced. However, after four such treatments her mental condition again worsened; she became once more excited and uncooperative and had screaming attacks and fits of falling to the ground, whereupon she was readmitted to a psychiatric hospital and given 10 more electroshock treatments. During this period her condition was diagnosed as a "schizophrenic reaction of paranoid type, with a depressive component but with lucid intervals"; considerable changeability in her mental state seems to have been observed. Physically, her condition was found to resemble Cushing's syndrome, though with a normal blood pressure (120/90). Examination of the cerebrospinal fluid at this time showed 51 mg. of protein per 100 cc., a flat colloidal gold curve, and a negative reaction to the Hinton test.

Examination.—Physical examination on admission to the Massachusetts General Hospital showed her to have fuzzy hair and a "moon-shaped" face. Her skin was dry, with a tendency to scale, and there was generalized hirsutism. She was somewhat obese, with wasted extremities, and had a "buffalo hump" of fat. There were ecchymoses on her shins, and her blood pressure ranged from 125/95 to 148/95. Neurological examination revealed generalized weakness of muscular origin and sluggish reflex responses, but no focal abnormality.

Laboratory studies showed a low lymphocyte count, a low fasting eosinophile count (9 to 11 per cubic millimeter), but no polycythemia. The blood-sugar curve revealed diminished tolerance. A roentgenogram of the skull showed a normal sella turcica, with no evidence of raised intracranial pressure, and no osteoporosis, either here or in the vertebrae, was present. Serum-potassium levels varied from 2.4 to 4.3 milliequivalents per liter, and the electrocardiogram was consistent with some intracellular hypokalemia. Excretion of 17-ketosteroids varied from 5.5 to 9.2 mg. in the 24 hours. Reexamination of the cerebrospinal fluid revealed a protein content of 124 mg. per 100 cc., an increased pressure (240 to 225 mm.) and a colloidal gold curve of 0001222000. The electroencephalogram was normal.

Mental State.—This was at first suggestive of schizophrenia in a state of partial remission. She exhibited little affect and fluctuating cooperation and at times laughed wildly for no good reason. With encouragement, she could be got to answer questions, and then showed a normal stock of information with no disorientation or impairment of memory.

During the subsequent few days her mental condition, though episodically variable, remained essentially similar to that described. Most of the time she remained quiet and withdrawn and made no spontaneous talk, but would give monosyllabic replies to questions. Her speech was slow and limited, and she smiled inappropriately on occasions.

Operation and Progress.—On Nov. 24, 1950, Dr. Oliver Cope resected an adenoma, of 3-cm. diameter, in the right adrenal. Her postoperative course was smooth, and she received treatment with corticotropin for a few days, until her blood pressure stabilized.

Within a few days of operation her mental condition underwent great improvement. She was quiet at first and continued to lack spontaneous speech for a time, but responded readily to questioning and seemed to be in much more contact with reality. This improvement continued, and she was discharged home just over one month after operation with no evidence of any severe mental disturbance.

The serum potassium levels rose after operation, and the electrocardiogram altered, suggesting an increase in intracellular potassium content. Examination of the cerebrospinal fluid, repeated just before discharge showed that the protein content had dropped to 37 mg. per 100 cc., and no abnormality was recognized. The fasting eosinophile count rose to from 55 to 80 cells per cubic millimeter, and the 17-ketosteroid-excretion level fell to between 1.2 and 1.6 mg. in 24 hours.

Follow-Up Study.—She was seen again three weeks, six weeks, and four months after discharge. On each occasion her mental state was apparently completely normal, and she stated that she felt that she was her "old self." During this period the physical abnormalities also disappeared, and her face became of normal appearance and contour. Her husband confirmed the improvement and said that she seemed to him to be better at this time than he had ever known her.

CASE 3 (M. G. H. 610989).—Miss J. D., aged 37, of Irish extraction, was admitted to the hospital on March 20, 1948.

Family History.—There was no record of mental illness or significant physical disease, and she had six siblings alive and well.

Previous History.—The patient's birth and childhood were described by an elder sister as normal, and she was said to have been a moderately good student. She emigrated to the United States in 1929, after which she worked as a nursemaid and a waitress. Her personality was described as a happy one; she was popular, made friends easily, and was strong, energetic, and cheerful in disposition. The only history of previous illness was that of measles, whooping cough and chickenpox in childhood.

Present Illness.—This commenced in Ireland, to which she had returned in 1939. Eighteen months before her admission to the hospital there developed backache and pains of a "rheumatic" nature in the limbs and joints. Three months later her menstrual periods ceased, and she experienced hot flushes.

She returned to the United States in October, 1947, whereupon her sister, with whom she came to stay, observed a great change not only in her physical appearance, but in her personality. Previously sociable, she had become seclusive and depressed and frequently took to her bed and refused to see people. Three months before her admission the pain in her back became so severe that she had to stop work, and during the final two months she had spent most of the time lying in bed to obtain relief from pain. In addition, it was noticed that her hair had become thinner and her face fuller, and her skin had begun to look and feel old and rough. However, only in the week before admission did the patient herself express anxiety over the changes in her appearance.

Physical Examination.—On admission she presented some obesity of the face, neck, and trunk, with sparing of the extremities; a thin, atrophic skin; an appearance of plethora, and kyphosis of the lower thoracic portion of the spine. Ulcers were present over both trochanters and the sacrum. Abdominal striae were absent, and there was no hirsutism, but the hair on her head was thinned. Neurological examination showed muscular weakness, and her blood pressure was 150/110.

Laboratory Studies.—There was slight polycythemia (red blood cells, 5,400,000 per cubic millimeter), and the fasting eosinophile count was low (3 cells per cubic millimeter). The fasting blood-sugar level was normal, but a blood-sugar curve showed decreased sugar tolerance. The serum potassium measured 5.1 mEq., sodium, 141.7 mEq., and chloride, 97 mEq., per liter, and calcium 9.3 mg. per 100 cc. Roentgenograms of the vertebrae showed marked osteoporosis with several compression fractures, and the roentgenogram of the skull revealed no abnormality other than osteoporosis. Excretion of 17-ketosteroids was 1.7 mg. in 24 hours. The cerebrospinal fluid was not examined in this case.

Mental State.—The patient was extremely depressed and retarded; her speech was slow and her face inanimate. She was apprehensive, feared she had cancer, and expressed strong guilt feelings. She was seen by Dr. Denis Leigh, who found her severely depressed, but noted that she was well oriented and that her memory for recent and past events was normal.

After her admission her mental condition worsened. At times she became agitated; on other occasions she exhibited little affect beyond apathy. She became convinced she had cancer, stated she was afraid to die because she could not face God, was hallucinated at times, and complained that the doctors were mocking her. She expressed no suicidal ideas, but when questioned directly said she was "dead already." On one occasion, she became convinced that the hospital was on fire, and she seemed to welcome the idea of such a conflagration.

Progress and Treatment.—On April 20, 1948, her left adrenal was explored by Dr. Oliver Cope, and a cortical adenoma measuring 3 cm. in diameter and weighing 12 gm., was excised. Her postoperative course was somewhat stormy and was complicated by massive collapse of the lower lobe of the right lung. Two weeks after operation she was considerably less retarded, but with the increase in her motor and psychic activity growing agitation was expressed. She continued to have fever, owing to a urinary infection, which ultimately responded to strepto-

mycin. Her blood pressure fell to about 100/70, and there were considerable vomiting and a decrease in serum sodium, potassium, chloride and protein, the condition improving after administration of desoxycorticosterone acetate and an increase in her food intake.

By May 31, her mental state was substantially unimproved, and the advisability of electroshock therapy was considered. However, after this date she started to improve spontaneously, and by June 27, 1948, both her physical and mental condition had undergone a remarkable change. Not only did she then appear physically normal, but she became cheerful, talkative, happy, and optimistic regarding her recovery. She was discharged from the hospital on July 2, 1948, 3½ months after admission.

Follow-Up Study.—She was seen 12 times as an outpatient during the next 2½ years and, except for a slight recurrence of the urinary infection, remained well and steadily gained strength. Her menstrual periods recommenced within a month of her discharge. Throughout the entire follow-up period she remained mentally normal, and it was noted that her old cheerful personality had reasserted itself.

CASE 4[15] (M. G. H. 93072).—Miss M. A., aged 25, an American-born white girl, of Greek extraction, was admitted to the hospital on June 14, 1949.

Family History.—There was no significant family history of mental or physical disease, and both parents and three siblings were alive and in good health.

Previous History.—Her birth, early development, and schooling were normal so far as was known. At the age of 18 she entered a conservatory of music, having planned to become an opera singer, but this career was interrupted by her joining the WAVES, at the age of 20. A photograph taken about this time shows her to have been a normal and attractive girl.

There was no previous medical history of significance.

Present Illness.—Her illness seems to have commenced in 1943, during her period of naval service, after six months of which she was discharged with a diagnosis of hysteria. After this discharge she was in the hospital for a time with a "nervous breakdown." She then attended a university for one semester but, finding herself unable to concentrate, gave up her study and worked for a time as a medical secretary.

In 1944 she found that she tired easily and had a tendency to gain weight, although her food intake had not increased. She then had another "nervous breakdown," during which she compained of generalized tremors and of "feeling foggy" at times.

In 1945 she still felt weak but was able to go back to, and carry on with, her work. She found that her skin was becoming rough and red and that pimples were developing upon her back, and she also noticed the growth of some hair on her chin and around her lips. She tried to attend the university again but was forced to give up again on account of inability to concentrate. In 1947 she became so weak that at times she could hardly climb stairs. She complained of aching pains in her back and pressure headaches in both temporal regions, and on occasions she felt retarded and drowsy. Menstruation also ceased at this time.

In February, 1948, she had a severe pain in her right flank, accompanied with hematuria, and was admitted to the hospital for investigation on this account, though no definite conclusions seem to have been reached. However, 11 months before admission to the Massachusetts General Hospital, she was found to have gained about 30 lb. (13.6 kg.) in weight and to have marked facial hirsutism. Both adrenals were explored, and the left adrenal was removed, after which she returned home, feeling a little better. She then entered a secretarial school but did poorly.

On Dec. 28, 1948, she was admitted to the Veterans Administration Hospital at Framingham, Mass.[15] She was very self-conscious about her appearance and complained of pain in her back, chest, and legs and of a sour taste in her mouth. She stated that at times she became very tense and felt she was "about to explode," and that on occasions she screamed and shook all over. She also felt that she was losing her equilibrium and was unable to walk in a straight line She stated she had noticed a tendency in herself to reverse words and to twist sentences. On examination at this time, she was described as being sluggish, with definite psychomotor

15. Drs. Jack D. Rosenbaum and William P. Nelson III, of the Veterans Administration Hospital, Framingham, Mass., allowed us to use their material in this case.

retardation, and her voice was said to be low in pitch. Her general appearance was that of Cushing's syndrome. Neurological examination showed no abnormality except for slight tremor of the extended fingers.

During her stay in this hospital, she was further described as nervous, subject to generalized tremors, at times liable to be easily upset, and as having minor hysterical reactions. A number of investigations were performed, the most striking of which was a pneumoencephalographic study, which was reported by Dr. Sosman as showing "a remarkable picture of diffuse marked cortical atrophy." His report continues: "There are marked generalized dilatation of the cerebral sulci and a moderate degree of generalized dilation of the ventricular system, with no displacement or deformity and no evidence of cerebrospinal fluid block."

A lumbar puncture was also carried out, and the cerebrospinal fluid was found to be under a pressure of 90 mm. and to have a protein content of 72 mg. per 100 cc. An electroencephalogram showed normal alpha rhythm in all leads, with the appearance of slow waves on hyperventilation. The results of chemical investigations were consistent with the diagnosis of Cushing's syndrome, except the blood-sugar curve, which was within normal limits. She was finally given 15 irradiations of the pituitary body and discharged, without appreciable improvement.

Examination.—Physical examination on admission to the Massachusetts General Hospital shortly afterward showed her to be a ruddy, "moon-faced," bearded young woman with some obesity, chiefly of the trunk, and a fair-sized "buffalo hump." Her skin was thin with numerous visible veins; she had acne on her back and chest, and there were purple striae on her abdomen and beneath her breasts. The pubic hair had a masculine distribution. There were bilateral edema of the ankles and bruising of both legs. Her blood pressure was 115/70, and the heart sounds were tick tack in quality.

Laboratory studies then revealed decreased sugar tolerance, a low lymphocyte count, and serum-potassium levels varying from 3.6 to 5.4 mEq. per liter. Excretion of 17-ketosteroids varied from 9.6 to 18.8 mg. in 24 hours. The electrocardiogram was within normal limits, but an electroencephalogram showed some instability on overbreathing, somewhat greater on the right side than on the left. Roentgenograms showed diffuse osteoporosis, but, apart from this, that of the skull was normal.

Mental State.—During her period of hospitalization she had several attacks consisting of twitching and jerking of all extremities, by their nature suggesting hysterical seizures. She also complained continually, particularly of pressure headaches, tremor, and weakness.

Her mental condition was reviewed in detail by Dr. Harley C. Shands. He found no evidence to suggest neurotic traits in childhood, difficulties in adolescent adjustment, or nervousness existing prior to the onset of her illness. He noted her present irritability and lack of self-control, her lack of drive and interest, and her inability to concentrate and make decisions. She had become somewhat meticulous, preferring not to do things at all if she could not carry them out perfectly, and was easily upset by any surrounding disorder. She stated that she no longer cared how she looked, and that her appearance was now so bad that nothing she could do made any appreciable difference. As a result, she thought that she had become sloppy and lazy.

Further Course and Treatment.—After investigation, implantation of a pellet of desoxycorticosterone acetate was carried out, and the patient was discharged from the hospital on July 17, 1949.

She was readmitted on Nov. 7, 1949, feeling considerably worse, hopeless, depressed, and despondent. She complained that her memory had deteriorated and that her thought processes had become even slower during the last few weeks. She also described having had more nervous spells, in which she shook all over and felt a desire to scream. Objectively, she was noted as depressed and retarded; her speech was slow, and she answered questions only after long pauses. She expressed agitation, said that she felt she must scream at times, and was concerned that her heart was stopping.

After further investigation, the right adrenal was explored by Dr. Oliver Cope. This was discovered to be enlarged several times, and about one-half was resected. The postoperative course was smooth; she started to lose weight rapidly and became less plethoric, and her strength, spirits, and appearance all improved. She was discharged from the hospital on Jan. 3, 1950, and an electroencephalogram at this time was normal.

After her discharge, however, there was a gradual return of all her complaints, particularly those of weakness, fatigue, and diffuse muscle and joint aches. On reexamination, she was found to retain the typical appearance of Cushing's syndrome. It was suspected that the remnant of her right adrenal had undergone hypertrophy; exploration revealed this to be the case, and a further 5.5 gm. was resected. Within a short time after this operation her physical condition underwent striking changes toward normality. Her mental state, on the other hand, seemed to deteriorate; she exhibited stubborn anorexia, became even more depressed, on one occasion complained of a hallucinatory experience during the night, and stated that people were trying to pull the dressing from her operative wound. Her blood pressure also fell considerably, and she was given desoxycorticosterone acetate and cortisone in order to control this.

One month after operation her depression lifted, and for the first time she volunteered the information that she felt improved. This betterment coincided with the beginning of desquamation of her skin and the failure of the hair on her upper lip, which she previously had had to shave, to reappear. She was discharged again from the hospital on June 7.

This, however, was not the end of her troubles. She was readmitted to the hospital on Aug. 23, 1950, again in a very upset and emotionally unstable condition. A reliable history was not obtained, but it seemed that within a short time after her previous discharge she had become weaker again, her aches and pains had recurred, and attacks of nausea and vomiting had been troublesome. Six weeks before, she had been admitted to another hospital on account of these symptoms but was transferred because of lack of improvement with treatment.

Physically, she presented a picture of hypoadrenalism. She had lost 40 lb. (18.1 kg.) in weight; her hirsutism had largely disappeared, and there were areas of brownish-black pigmentation on her face, nipples, and lips, and in the palmar creases, suggesting Addison's disease. She said she had had two menstrual periods since her last operation. Mentally, she was described as emotionally unbalanced and in a state resembling hysteria. Laboratory investigations confirmed that her condition was then one of hypoadrenalism, and she was given treatment with cortisone, desoxycorticosterone acetate and methyltestosterone, on which regimen her condition rapidly improved, and she was once again discharged.

Follow-Up Study.—She was seen as an outpatient on three occasions during the next six months. Her physical and mental improvement was maintained; she looked nearly as well as she had before her illness began and stated that she felt well. Eight months after admission she seemed in fairly good health, though there was some question whether her adrenal insufficiency was completely controlled, but on closer questioning it became clear that her mental state, although much improved, was not altogether normal. She stated that she was still easily upset by the comments of others, was inclined to be restless and irritable, became depressed at times, and was generally less interested in her environment than she felt she should be. She thought that her memory had improved and that she was quicker to learn than she had been. However, on tests she was unable to retain seven given digits, nor could she repeat correctly more than four in reverse. Subtraction of 7's from 100 took her 2½ minutes, though she only made one error. It was believed that her condition indicated some degree of cerebral impairment, though the full extent could not be determined, while the question of adrenal insufficiency and the possible effects of this upon cerebral function remained unsettled.

Case 6 (M. G. H. 659364).—Mrs. D. O'B., aged 33, a Canadian-born housewife, was admitted to the hospital for the first time on April 25, 1949.

Previous History.—Her previous medical and social histories were normal. The family history contained nothing of significance save the fact that one brother had become somewhat nervous after a period of war service. She was married and had two children, and her husband described her premorbid personality as a warm and happy one.

History of Illness.—The present illness began 2½ years before her admission with the onset of severe bitemporal headaches. There then developed hirsutism, which became marked, obesity of the face and trunk, characteristic skin changes, and easy bruisability, as well as increased appetite, polyuria, and hypertension. Menstruation was unaffected.

Examination.—Examination on admission showed the classic features of Cushing's syndrome. There were hypertension (blood pressure, 220/115 to 230/130), polycythemia, glycosuria, and decreased sugar tolerance. Other chemical investigations revealed hypochloremic, hypokalemic

alkalosis. The roentgenogram of the skull was normal except for some decalcification of the clinoid processes and the bones of the vault. Examination of the cerebrospinal fluid showed a normal pressure, 2 cells per cubic millimeter, and a protein content of 41 mg. per 100 cc.

Progress and Treatment.—During her first admission the right adrenal gland was explored by Dr. Oliver Cope and found to be hyperplastic. A hemiadrenalectomy (right) was performed. She recovered uneventfully from this, and, after a course of irradiation of the pituitary, was discharged from the hospital, somewhat improved. She was followed over the next two years, during which a further course of irradiation to the pituitary was given.

In March, 1951, her appearance was noted as substantially unchanged, and, as she was still troubled by pressure headaches and moderately severe headaches, she was readmitted for further surgery. On this occasion a total adrenalectomy was carried out on the left side, followed within a short time by a second subtotal resection of the right adrenal. It is as yet too early to say what the final result of this treatment will be.

Psychiatric Symptoms.—Prior to her illness she had always been of cheerful disposition, a happy, sociable person who enjoyed life and who had never considered herself as nervous. However, through the course of her illness she complained of periods of depression and nervous irritability. She related how she would snap at her husband for little reason and become easily intolerant of noise or mischief on the part of her children. She had frequent crying spells, particularly when she was on her own, and complained of constant lack of energy and of feeling "washed out." She was able to get through her housework, though not without difficulty. She slept poorly, being disturbed by slight noise, unpleasant dreams, and a frequent desire to micturate. There was no loss of libido, and her sexual relationship with her husband remained satisfactory.

On examination she appeared alert and friendly and exhibited a warm affect. She made little complaint beyond headaches, which were troublesome. She was not noted as overtly depressed and showed no psychomotor retardation.

Her husband, however, confirmed the patient's mood changes but stated that he thought these were the result of anxiety due to the changes in her physical appearance. She herself stated that she was considerably worried by the somewhat gross alteration in her appearance, as a result of which her friends would at times pass her in the street without recognition. She was, nevertheless, positive that her anxiety about this, although considerable, was insufficient to account for her periods of depression and irritability.

CASE 24 (M. G. H. 387969).—Mrs. R. K., aged 32, an American-born housewife, was admitted to the hospital on Jan. 24, 1951.

Previous History.—Her previous medical history contained nothing of importance. There was no family history of nervous or mental disease except that one sibling had died in infancy with convulsions. One other sibling had been killed accidentally, and three others were alive and well. A maternal uncle and aunt both had diabetes.

History of Illness.—The illness seemed to have begun after the birth of her first baby, three years prior to admission. She gained 50 lb. (22.7 kg.) during the pregnancy and after the birth was unable to lose weight. During the year before her admission to the hospital, menstruation had become irregular, and for five months before admission she had had complete amenorrhea. When first seen in the outpatient department in November, 1950, she was thought to be pregnant. She complained of many other symptoms, such as acne, easy bruisability, further increase in weight, a ravenous appetite, polydipsia, and polyuria, described herself as a "complete nervous wreck," and said that she constantly felt as though someone were strangling her.

Physical Examination.—She was obese, swarthy, and hirsute and had a prominent abdomen, characteristic skin changes, and a general appearance altogether typical of Cushing's syndrome. Moderate hypertension was present (blood pressure 178/98); there was a decreased sugar-tolerance curve, and x-ray studies showed slight spinal osteoporosis and a stone in the right kidney. Examination of the cerebrospinal fluid at this time revealed a normal pressure, an increased protein content (144 mg. per 100 cc.), and a colloidal gold curve of 0001221100.

Progress and Treatment.—On Jan. 19, 1951, exploration of the adrenals was carried out by Dr. Oliver Cope, and a benign adenoma, measuring 4 by 4 cm., was removed from the right side. She made an uneventful recovery and was discharged within a few days. A second exami-

nation of the cerebrospinal fluid just prior to her discharge showed that the protein level had now dropped to 46 mg. per 100 cc. After discharge, however, she continued to complain of nausea and vomiting, and because of this, and the development of other, odd symptoms, she was readmitted a short time later for further observation. During this admission it was found that the signs of Cushing's syndrome were rapidly receding. It was also discovered that she was about four months pregnant. Her complaints rapidly subsided, and she was again discharged within a few days.

Psychiatric Symptoms.—During the onset of her illness and for some time after operation, she complained of various psychiatric symptoms, and her self-description as a nervous wreck has already been mentioned. In addition to this, and the strangling sensation also alluded to, she described a number of other odd symptoms, such as a sensation of swelling of her tongue and impairment of her sense of taste, which complaints were not objectively confirmed. In addition, she slept poorly, possibly on account of nervousness and nocturia. On examination, she was noted to be depressed and retarded, especially in her speech and expression. After operation her nervous symptoms increased; her depression and retardation became more pronounced; she complained of various aches and pains and said that she felt lifeless.

Prior to her second admission, there developed twitching movements of her legs, some ataxia, and periods of emotional lability, during which she would cry and laugh without good reason. While she was in the hospital, all these complaints subsided rapidly except for a slight degree of depression and retardation. After discharge she continued to be somewhat improved, though she still complained of odd symptoms, such as twitching of her legs in bed, for which no cause could be demonstrated. Her husband commented on the striking up-and-down course of her symptoms after operation.

NEUROPATHOLOGICAL ABNORMALITIES

In addition to a study of the psychiatric manifestations and personality changes in this series, neuropathological investigations were carried out on some of the patients. Unfortunately, these investigations are insufficient to allow any definite conclusions to be drawn as to the relation between the abnormalities discovered and the mental symptoms. They have been included, however, because the findings have been thought to be of some importance and because of the relation of these findings to those in certain cases described by other authors.

The cerebrospinal fluid was examined in nine cases. In six of these (Cases 2, 4, 11, 22, 24, and 25) an increased total-protein content, varying from 51 to 144 mg. per 100 cc., was discovered. In the other three (Cases 1, 6, and 13) the total-protein levels were 40, 41, and 32 mg., respectively, per 100 cc. In two of the three cases in which a reexamination of the spinal fluid was made after operation, and in which the patients were in the process of recovery, the protein content was found to have fallen considerably—from 124 to 40 mg. per 100 cc., in Case 2, and from 144 to 46 mg. per 100 cc. in Case 24. In the former case the second lumbar puncture was performed three weeks, and in the latter five days, after operation. In the third case (Case 1) the protein content was found to be high normal both before and after operation (40 and 39 mg. per 100 cc., respectively). In addition to the changes in the total-protein content, slight, and probably insignificant, changes in the midzone of the colloidal gold curves were found in five of the seven cases in which the Lange test was made. The most marked of these was in Case 11, in which the total-protein content of the cerebrospinal fluid was 76 mg. per 100 cc. and the Lange curve 0012332100.

The cerebrospinal-fluid pressures in these nine cases ranged from 90 to 240 mm. of water, and in only two (Cases 2 and 25) was the pressure higher than 200 mm.

X-ray studies of the skull were carried out in most of the cases, but in none was any significant abnormality observed. In two (Cases 7 and 9) a rather large sella turcica was seen, while in one (Case 11) there was evidence of erosion of the anterior and posterior clinoid processes and thinning of the dorsum sellae. The only fairly constant finding was that of osteoporosis, which in many cases was seen in the skull, as well as elsewhere. In the one case in which a small pituitary tumor was discovered at autopsy (Case 5) the roentgenogram of the skull prior to death showed no abnormality.

A pneumoencephalogram was performed in one case only (Case 4). This, which was markedly abnormal, has already been described, and its possible significance will be discussed later.

Electroencephalographic studies were carried out in four cases. In two of these (Cases 1 and 2) the records showed no abnormality despite severe mental disturbance at the time of the recording. In another (Case 4) the record was abnormal while the Cushing syndrome was severe and there was much mental disturbance, became normal during resolution, and then was abnormal again during the period of hypoadrenalism which followed. In the remaining case (Case 25), in which mental symptoms were mild to moderate, but in which drowsiness was a prominent symptom, there was a mildly abnormal record with rare 2.5- to 6-per-second waves, most marked in the left temporal region, though also visible on the right.

In seven cases an autopsy was performed, but in only four was the brain examined. In one (Case 5), in which a small basophile adenoma was found, death was the result of a massive cerebral hemorrhage following partial remission of her symptoms. In another (Case 23), in which mental symptoms were only mild, death was due to secondary metastases from an adrenocortical carcinoma, and at autopsy the brain was found to weigh only 980 gm. The lateral and third ventricles were considered somewhat enlarged, though no other definite abnormality was observed; and microscopic examination was not carried out. In the two remaining cases (8 and 18), those of a cortical adenoma and a cortical carcinoma, respectively, the brains were thought to be normal, and microscopic examination of the hypothalamus in the second case showed nothing remarkable.

In no case did neurological examination reveal any significant abnormality, although certain symptoms, such as headache, tremor, drowsiness, and numbness and tingling of the extremities, were complained of by some of the patients and may possibly be ascribed to neurological or intracranial disease. In one case muscular weakness was so extreme that the possibility of a muscular dystrophy or polyneuritis was considered, only to be later excluded. Ophthalmoscopic and perimetric examinations were carried out in many of the cases. No alterations in the visual fields were observed, and the fundi were normal except in four cases, in which some degree of hypertensive retinitis was present.

RESULTS OF TREATMENT

The results of treatment on the physical and, particularly, the mental status of these patients is of considerable interest.

Seven patients died—four (Cases 7, 8, 12, and 18) postoperatively and two others (Cases 13 and 23) of carcinoma. These cases will not further be considered.

One other patient (Case 5) had a partial remission of the symptoms of Cushing's syndrome but died later of a cerebral hemorrhage, though there was evidence of some mental, as well as physical, improvement prior to death.

One patient (Case 11) probably still needs further surgical treatment, and for two others (Cases 6 and 25) it is as yet too early to assess the adequacy of treatment. In one of these patients, who had severe hypertension, this disability still persists.

In the 15 other patients for whom treatment seems to have been adequate and successful in alleviation of their physical disease, some assessment of mental recovery may be made. Three of the patients with severe mental disturbance (Cases 1, 2, and 3) appear to have recovered within five weeks, a few days, and nine weeks, of operation, respectively. M. C. (Case 2) has been followed for 4 months, and J. D. (Case 3) for 2½ years, and in neither is there now any sign of mental illness or of physical disease. R. A. (Case 1) has so far been followed one month only, and her emotional abnormality, although probably still present to some degree, continues to improve as her physical disability resolves. M. A. (Case 4), who was also severely disturbed, has undoubtedly shown considerable improvement in this respect. Her retardation, most of her depression, and many other psychiatric symptoms of long standing have disappeared concomitantly with the resolution of the Cushing syndrome. She retains, however, considerable emotional lability, has not yet been able to hold a job for any length of time, and shows evidence of cerebral impairment. Her physical status at the moment is one of partially controlled hypoadrenalism.

R. B., S. W., B. V., and R. K. (Cases 14, 17, 22, and 24), all of whom had moderately severe personality changes, have shown some degree of recovery. R. B. (Case 14) was noted to have become more alert mentally when the Cushing syndrome was considered no longer active. S. W. (Case 17) remained irritable and complaining for 18 months after her second operation, but finally admitted considerable improvement about 10 months after it was considered that her physical condition had become normal. B. V. (Case 22), who, like R. B. (Case 14), was treated largely by irradiation, improved several times during the course of her long illness, only to become more irritable and nervous during physical relapses. At one stage of improvement following a course of irradiation of the pituitary, the improvement in her mental status was remarked upon by her family, who stated that she had become much more alert and responsive than she had been previously. This patient later became a chronic invalid, owing to congestive heart failure, although the Cushing syndrome was no longer considered active. R. K. (Case 24) has continued to improve erratically after operation, though for a time her mental disturbance became even worse than before this procedure. This patient was also disturbed by pregnancy, with which she was unwilling for a time to continue, and has so far been followed for only three months after leaving the hospital.

Of the remaining seven patients, one (Case 9) still has a mild Cushing syndrome, but his condition has much improved, both physically and mentally, and he is able to carry on a busy practice as a dentist. Little is known about the present condition of one other patient (Case 10), as he has refused to attend for follow-up observations. His original condition is believed to have resolved, but he is thought to have hypoadrenalism. He was described by his physician as a "neurotic" person,

in whose present condition there is a psychiatric component which is hard to evaluate. The other four patients (Cases 16, 19, 20, and 21), who manifested little or no significant mental abnormality during the course of their illness, have all recovered as far as their physical condition is concerned.

None of the patients in the series, except M. C. (Case 2), who received a considerable number of electroshock treatments elsewhere, without effect, and before the true nature of her condition was realized, received any specific treatment for mental disturbance.

POSSIBLE ETIOLOGICAL FACTORS

The obvious possibilities are the effects of disordered endocrine function upon the mental status, psychological reactions to disfigurement, discomfort, and chronic semi-invalidism, all of which will be discussed. Beside these, certain other factors in the lives of these patients have to be considered, not only in view of their possible relation to personality change but also because they may play a part in the production of the endocrine dysfunction itself.

Cushing's syndrome is predominantly a disease of women. This observation is borne out by the present series of 25 patients, only 3 of whom were men. This leads to consideration of whether or not certain stresses peculiar to the female sex, namely, pregnancy, childbirth, and the menopause, all of which produce psychological effects, as well as alterations in the physical and endocrine status, may play an important part.

Thirteen of the 14 married women in the series were parous, and in 9 of these the illness seems to have commenced within three or less years of childbirth. The other four did not have onset of their illness until the time of the menopause or after. In three of the patients (Cases 7, 8, and 24) the illness actually commenced directly after a pregnancy, and all three patients had further pregnancies during the course of the disease. B. Ab. (Case 7) became obese during the first pregnancy, was afterward unable to lose weight, and, after a second pregnancy two years later, followed by the death of her baby at the age of 4 months, had a "nervous breakdown" and manifested frank signs of Cushing's syndrome. In M. d'A. (Case 8) the illness seems to have developed about the time of the first pregnancy, which ended in a miscarriage. This patient had three other pregnancies, the first of which was terminated prematurely by Caesarean section, owing to the development of toxemia. R. K. (Case 24) also failed to lose weight after a pregnancy three years before admission to the hospital and then had gradual development of signs and symptoms of Cushing's syndrome, which increased in severity when she became pregnant again, about the time of admission. It is perhaps noteworthy that even after removal of a cortical adenoma she expressed a frank desire to have the pregnancy terminated. In the other six patients (Cases 1, 2, 5, 6, 11, and 21) the time association between the onset of the disease and childbirth was less direct, the interval between the puerperium and the initial symptoms being 3 years for two of the patients, 2½ years for two others, and about 12 and 6 months, respectively, for the remaining two. It is pointed out, however, that the onset of the disease is often insidious and difficult to determine and that, were a greater degree of accuracy possible in this respect, the time relationship might be a more positive one.

Lest too much weight be placed on pregnancy as an etiological factor, due consideration must be given to the fact that the disease is especially liable to occur in younger women within the childbearing age limits. In addition to the married women with children, seven nulliparous women of childbearing age, only one of whom was married, and one female child were found in this series. Comparison of the ages at onset of the disease, as far as this can be ascertained in the two groups, reveals that there was a much wider range within the nulliparous group, whose ages of onset (excluding that of the child) extended from 18 to 40, than in the group of parous women, whose ages of onset ranged from 24 to 33. Both groups are too small to permit any significant conclusions to be drawn, but the relatively narrower age range of the numerically larger parous group, as well as the fairly close relation of the time of onset of symptoms to that of a previous pregnancy, to which attention has been drawn, suggests that pregnancy and childbirth may represent a physiological and psychological stress which may precipitate a latent defect in some cases.

Among the older patients, two of the parous women (Cases 14 and 16) became ill at the time of the menopause, and in another, childless patient (Case 13), who had had her uterus removed at the age of 26, Cushing's syndrome developed as a result of an adrenal carcinoma 25 years later. Two other patients, both married and with children (Cases 18 and 25), the first of whom also had an adrenal carcinoma, had the appearance of symptoms 11 and 13 years, respectively, after the menopause.

A number of the patients with Cushing's syndrome had other diseases of some severity. Three (Cases 8, 23, and 25) had gallstones or gall bladder disease, and on all three a cholecystectomy was carried out. The first of these died of complications of this operation. Two (Cases 13 and 16) had extensive pelvic operations, and the former, in addition to removal of the uterus for endometriosis in early adult life, had previously had a fibrocystic tumor removed from her breast; furthermore, at the time of development of the Cushing syndrome she had a moderately severe rectovaginal fistula, which made her incontinent of feces on occasions. The initial symptoms of her endocrine illness were nervousness and anxiety, for which she received treatment from her physician. Another patient (Case 17) had obliterative arterial disease of the legs at the time of onset of her other symptoms, though the relation of this condition to Cushing's syndrome is difficult to determine.

Psychological stress was a possible etiological factor in some of the cases. In Case 4, as has been recorded, the initial symptoms were those of a nervous illness, thought to be of a hysterical nature, which occurred while the patient was in service with the WAVES. In Case 5 the commencement of the illness coincided with a divorce, following a period of marital disharmony. In Case 7 a "nervous breakdown," coinciding with the death of the patient's second baby during infancy, has been mentioned. In Case 12 the patient had severe social and domestic problems; her mother was crippled with long-standing rheumatoid arthritis; in addition to working as a mechanic, this patient had to look after and manage a household, which, besides her parents, contained three siblings. This patient, who was engaged to be married, is also said to have broken off her engagement on account of the illness. R. B. (Case 14) was the only one who had a family history

of mental disease. One of her sisters had had a nervous breakdown, and another had been an inmate of a state hospital for mental diseases for many years. This patient's illness is interesting, since it not only developed at the time of her menopause, but followed her husband's coronary thrombosis, an event which incapacitated him to the extent that he had to give up his business, with the result that straitened financial circumstances forced the family to go on relief.

Of the remaining eight patients, only one of whom had severe mental symptoms (Case 3), another (Case 22) being moderately disturbed, little is known of possible precipitating factors. Two of the three men (Cases 9 and 10) manifested their first symptoms while on overseas service with the armed forces, one while on Guadalcanal.

Investigation of other constitutional or hereditary factors revealed little of significance. The patients were drawn from widely differing social levels, and their racial origins were extremely diverse. No specific tendency toward any particular type of disease, including endocrine disorder, was apparent from the family histories. One family, that of Case 23, was possibly prone to diabetes, while the relatives of two others (Cases 15 and 17) showed a tendency toward obesity. It is perhaps noteworthy that the father of R. A. (Case 1) was a short, stocky, round, red-faced man, whose appearance in some ways greatly resembled hers, but who denied, however, that his health was anything but good. The family history of mental illness in Case 14 has already been mentioned.

No inference can be drawn from these largely negative findings because of the retrospective method employed in the assessment of many of the cases. Many details which might have thrown light on possible hereditary or constitutional factors were, unfortunately, lacking from the records.

COMMENT

Consideration may now be given to the nature and origin of the mental disturbance not uncommonly associated with this syndrome.

It is obvious that no single clear-cut psychiatric picture emerges from the galaxy of mental symptoms that these patients present. If to these be added the manifestations described by other authors,[16] the catalogue of symptoms becomes so extended as to cover a large part of the total range of known psychiatric phenomena.

Depression of some degree, often, though not invariably, associated with retardation, is perhaps the state most frequently encountered. Retardation, when absent, appears to be replaced by irritability in the form of agitation, anxiety, crying spells, or noncooperative behavior, or both retardation and irritability may appear in the same patient at different times. However, the variability of mental symptoms in these patients is so marked that Soffer's statement, that mental changes when present are in general similar, needs qualification.[3]

Variation in the clinical psychiatric picture not only is seen from patient to patient, but also occurs strikingly in the course of the disease in any one patient. This is well shown by the fluctuation of mental symptoms in Case 1 of this series,

16. (*a*) Altschule, M. D.: Bull. New England M. Center **11**:229, 1948. (*b*) Cushing.[1] (*c*) Kepler and Locke.[2c] (*d*) Lintz.[6] (*e*) Maclay and Stokes.[5]

especially during the phase of postoperative recovery of her illness, during which she was frequently subject to episodic outbreaks of increased depression, agitation, and diminution of insight, of temporary nature and without apparent exciting cause.

Both variation from patient to patient and variability in the nature of mental symptoms in a single patient also appear to be characteristic of the mental disturbance which sometimes occurs in association with corticotropin and cortisone therapy. Here, also, depression seems to be the commonest phenomenon, often associated with pronounced irritability and the expression of paranoid ideas. Sudden exacerbation in the severity of mental symptoms without apparent exciting cause is probably even more striking in these cases than in cases of Cushing's syndrome, and a mental picture which is largely depressive in appearance may undergo a sudden transition to one which more closely resembles a schizophrenic state. These cases bring to mind the difficulty sometimes encountered in the exact diagnosis of other types of psychotic disturbances not overtly associated with endocrine dysfunction, which has led in part to the application of the term schizoaffective disorder to many such forms of illness.

There is a relation in most cases of Cushing's syndrome between the onset of bodily changes and the occurrence of mental symptoms, though either may seem to precede the other or the two may appear simultaneously. Schlezinger and Horwitz [9] believe that physical manifestations usually precede alterations in the mental state, although they note that the reverse is true in the case they themselves describe. In the present series of cases, however, psychiatric symptoms were usually among the first to make their appearance, especially in those four patients (Cases 1 to 4) who exhibited the greatest degree of mental disturbance. The mental symptoms of these patients appeared at a stage at which the characteristic physical changes, though they had begun to appear, were barely striking enough to allow immediate recognition of the true nature of the condition, at least to the less experienced diagnostic eye. In Case 2, for example, the patient was for some months thought to be schizophrenic, and, as a result, received a considerable number of electroconvulsive treatments before the correct diagnosis was actually made, while in Case 4 rather severe mental symptoms preceded the occurrence of any definite physical changes for almost a year. The same held true, though to a less extent, in other cases with a more moderate degree of mental disturbance, though in all cases the severity of the mental symptoms seems to have increased in relation to the progress of the physical disease. This should not be taken to indicate that severe mental illness is more liable to occur in those cases in which the physical changes are grossest, merely that if mental symptoms are present these will probably increase in severity as long as the physical disorder is allowed to progress unchecked. R. A. (Case 1), for example, who was severely disturbed, although having a typical Cushing's syndrome in many respects, was not grossly disfigured by her condition, nor were the chemical and metabolic changes particularly profound. Other patients with severer physical symptoms showed proportionately much less mental disturbance, while in many patients, as has been seen, mental symptoms were either insignificant or absent.

A further analogy can be drawn here with cases of corticotropin and cortisone psychoses, in some of which many of the physical changes associated with Cushing's

syndrome have been described,[17] but in which frequently there is severe mental derangement without apparent physical alterations. In assessing these cases, however, the original disease for which corticotropin or cortisone has been prescribed must doubtless be taken into account. Furthermore, the susceptibility of the individual patient to the effects of corticotropin or cortisone is subject to much variation and does not bear a direct relation to the dosage or to the length of time during which the drugs are administered, apart from the fact that there would seem to be an ill-defined threshold which must be exceeded before mental symptoms can be expected occasionally to occur. Indeed, one of the most striking features of the mental reaction sometimes encountered in response to these therapeutic agents is found not only in the relation between time of onset and dosage but also in the variation in severity of the reaction and its prolongation after the offending drug has been withdrawn. This indicates that the limits of individual susceptibility are wide, especially as some patients become much disturbed by a low dose with relatively short administration. If a parallel does exist here, this explanation would also hold good for the inconstancy of occurrence of mental disturbance with Cushing's syndrome.

Abolishment of the adrenal hyperfunction by surgical removal of a tumor, by subtotal resection of the adrenals, or possibly in certain cases by irradiation of the pituitary relieves not only the physical and metabolic abnormalities, but also the mental disturbances. This, of course, excludes certain cases in which gross, and presumably irreversible, damage has occurred within the central nervous system, though it is probable that even in these patients some mental, as well as physical, improvement may be expected with adequate surgery, especially if the diagnosis is made reasonably early and treatment is sufficiently prompt. Patients who develop hypoadrenalism after treatment, in whom for some reason substitution therapy is inadequate, may be expected to show continued mental abnormality, though possibly in a different form.[18] Again, an analogy can be drawn with the reactions occurring with corticotropin and cortisone, which it appears subside spontaneously after cessation of therapy, though the length of time before resolution occurs is both highly variable and quite unpredictable.

In only two of the cases in this series was there evidence of a cerebral lesion; the abnormal pneumoencephalogram in Case 4, showing ventricular dilatation and cerebral atrophy, and the shrunken brain with some ventricular enlargement discovered at autopsy in Case 23 will be recalled. Both these findings are somewhat isolated, and therefore difficult to assess. Their importance lies in their comparability to similar changes described by others, and mention has already been made of Heinbecker's and Pfeiffenberger's observations[19] in this respect. The pathological abnormalities described by these authors in a number of cases include internal hydrocephalus of mild but definite degree, atrophy of the cerebral convolutions, atrophy of the ependymal cells of the third ventricle and thinning of its floor, and, particularly, atrophy of the paraventricular nuclei of the hypothalamus. Heinbecker held that the latter change is secondary to the chronic internal hydrocephalus, which at first causes depression of hypothalamic function and later demonstrable, and presumably irreversible, changes in these nuclei. He also believes that functional

17. Sprague, R. G.: Am. J. Med. **10**:567, 1951.

18. Gorman, W. F., and Wortis, S. B.: Dis. Nerv. System **8**:267, 1947.

19. Heinbecker.[10] Heinbecker and Pfeiffenberger.[11]

alterations in the hypophysis, which may be a cause of Cushing's syndrome, are due to the hypothalamic damage. The cause of the hydrocephalus is uncertain, but it is thought that it may result from raised intracranial pressure, due either to increased secretion or to diminished absorption of the cerebrospinal fluid. However, it is somewhat difficult to distinguish cause and effect here. Further light has recently been thrown on the matter by the experimental work of Castor and others,[20] who gave large doses of corticotropin and cortisone to rats, after which microscopic examination of the hypothalamus and parts of the thalamus and cerebral cortex was carried out. They found consistent cytological changes in the paraventricular nuclei of the hypothalamus of all rats treated with corticotropin and similar changes in some of the thalamic nuclei in certain animals, while one animal had swelling and chromatolysis of the large ganglion cells in the stratum ganglionare of the neocortex. The changes found in those rats that had been given cortisone were more widespread and of a somewhat different character, though the hypothalamic and thalamic nuclei again showed evidence of damage. As a result of these investigations, the authors conclude that degeneration of the paraventricular nuclei is a result of hyperadrenocortical activity, and not a cause of the disease, as Heinbecker suggested. Furthermore, the neuropathological changes which Heinbecker has recorded in patients with Cushing's syndrome do not seem to have occurred in patients with an adrenocortical tumor, but only in those with adrenal hyperplasia. In the present series it is clear that mental disturbance of all degrees of severity was seen almost as frequently in association with tumors of the adrenal cortex as with hyperplasia, and such difference as does exist might well have been absent or reversed had not the total number of patients in whom hyperplasia was the anatomical diagnosis somewhat exceeded that with adrenal tumors. In passing, attention may be drawn again to Case 23, in which some degree of cerebral atrophy was demonstrated at autopsy, if only to point out that in this case the principal lesion was a carcinoma of the adrenal cortex. However, no further inference can be drawn, for other information is lacking and no histopathological examination of the brain was made.

In Maclay and Stokes's case,[5] that of a woman aged 29 with Cushing's syndrome and mental symptoms of a depressive nature, autopsy revealed bilateral hyperplasia of the adrenal cortex, slight atrophy of the frontoparietal convolutions, and diminution in the number of the basophile cells of the pituitary, the last change presumably being due to antemortem insertion of radon seeds. Dilatation of the ventricular system or other pathological abnormalities were, however, not recorded. In the case of Schlezinger and Horwitz[9] an adenoma of the adrenal cortex was found, and further examination revealed Crooke's changes in the basophile cells of the pituitary. In addition, there were prounced congestion and edema of the brain parenchyma and focal areas of encephalomalacia in the frontal lobes. In life, the patient had, in addition to Cushing's syndrome, severe depressive symptoms and some signs of extrapyramidal motor disorder.

In another recent case, occurring elsewhere,[21] also with mental changes, a basophile adenoma of the pituitary was discovered. In life, a ventriculogram showed

20. Castor, C. W., and others: Proc. Soc. Exper. Biol. & Med. **76**:353, 1951.

21. The autopsy material in this case, that of a patient at the New England Center Hospital, was shown to one of us by Dr. H. E. MacMahon and Dr. J. S. Campbell, who permitted us to refer to their findings.

marked dilatation of the third and lateral ventricles and deviation of the third ventricle posteriorly. At autopsy the ventricular distension was confirmed; the brain was large and compressed, and there was flattening due to compression of the superior corpora quadrigemina, the cerebellum, and the pineal body. Histologically, there were some gliosis of the ependyma of the third ventricle and patchy edema of the brain parenchyma. The cause of the internal hydrocephalus was unexplained; the pituitary tumor, being only 0.5 cm. in diameter, was of insufficient size to have caused mechanical obstruction of the cerebrospinal-fluid circulation, a fact well demonstrated by examination of the pituitary fossa, which, except for slight erosion of the posterior clinoid processes, was normal. Despite still commonly held ideas to the contrary, basophile adenomas, when they occur, are small, and it is therefore doubtful whether such a tumor can, if ever, give rise to pressure effects.

Before leaving the subject of the relation of Cushing's syndrome to cerebral damage and psychic disturbance, some reference may be made again to the views of Oldenberg and other Continental authors [22] who have drawn attention to what they believe is a resemblance between the psychic disturbance of Cushing's syndrome and postencephalitic personality disorders. The evidence presented is not convincing; furthermore, we believe that there is on the whole an overfrequent tendency to explain any psychic or endocrine disorder of obscure origin by postulating a past history of encephalitis, even in the absence of a history of this disease. All that can be said concerning the present series of cases is that in none of them were there any neurological findings resembling the effects of encephalitis, nor was there a history of this disorder in any. In addition, the psychiatric disturbance observed, except for an occasional tendency to somnolence, does not particularly resemble the mental disorder following in the wake of encephalitis. Finally, the degree of mental recovery which occurs after surgical correction of the adrenocortical hyperfunction would appear to exclude encephalitic cerebral damage, for if this were a cause such a degree of resolution could not be expected as a result of adrenal surgery alone. However, in view of the protean manifestations of encephalitis, it would be reasonable to suppose that this ailment may be an etiological factor in occasional cases.

Whether or not corticotropin and cortisone can cause permanent cerebral damage largely remains to be seen, though there is growing evidence of such a possibility. A recent report [23] describes the occurrence of status epilepticus in 3 of 40 children treated with corticotropin for various complaints. In two of the three cases mental symptoms preceded the occurrence of the convulsive state, and in one case severe personality change, psychomotor seizures, aphasia, and apraxia persisted during the year in which the patient was afterward followed. In an unpublished case,[24] in which a boy aged 5 years with rheumatic fever was treated for eight days with cortisone, a convulsive state also developed, followed by a condition of decerebrate rigidity.

The association of adrenocortical dysfunction, metabolic abnormalities, and mental illness is a subject of growing interest. Cushing's syndrome implies pro-

22. Oldenberg,[4] Wolf, D.: Schweiz. Arch. Neurol. u. Psychiat. **56**:144, 1946.

23. Dorfman, A., and others: Status Epepticus Coincident with Use of Pituitary Adrenocorticotropic Hormones: Report of 3 Cases, J. A. M. A. **146**:25 (May 5) 1951.

24. Albright, F.: Personal communication to the authors.

found alteration in the metabolism of water, electrolytes, sugar, and protein; and most of the familiar physical changes are a direct result of these metabolic abnormalities.[2c] It is not to be supposed that the nervous system can escape the effects of such biochemical disorganization; rather, the reverse is to be expected. Extensive investigation of the metabolic state of patients with chronic psychoses has been carried out by Altschule,[16a] and other studies dealing with alterations of pituitary-adrenocortical function in patients with schizophrenia, involutional melancholia, and other severe personality disturbances are recorded by Hoagland and Pincus.[25]

Altschule found that the changes in carbohydrate and protein metabolism in patients with chronic psychoses resemble those seen in Cushing's syndrome, there being, among other changes, impairment of glucose tolerance with a normal fasting blood-sugar level and insulin resistance, together with hypercreatinuria, a lowered blood-glutathione level, and decalcification. Furthermore, the author believes that there may be a causal relation between the alterations in carbohydrate and protein metabolism seen in patients with chronic psychoses and the psychosis itself, an opinion based on the giving of corticotropin to normal persons, which if administered in large enough doses causes similar metabolic changes, as well as mental disturbance. Also, electroconvulsive therapy, which may cause improvement in the mental state of psychotic patients, may, according to this author, result in lessening of the impaired glucose tolerance and in other parallel improvements in metabolism.

Among the alterations in electrolyte metabolism seen in Cushing's syndrome, that of potassium metabolism demands especial attention. Hoagland [26] has recently reviewed some of the evidence relating potassium metabolism to adrenocortical function, on the one hand, and the function of the nervous system, on the other. He states that homeostasis in the concentration of brain potassium is to be expected in association with optimal brain function, and that this may be abnormally modified if the concentration of brain potassium is elevated or depressed. Examination of serum-potassium levels was carried out extensively in most of the cases in the present series, and some degree of hypokalemia was a frequent finding, though no specific correlation between an abnormally low serum-potassium level, or fluctuation in this, and the occurrence, exacerbation, or remission of mental derangement was observed; nor was there any clinical evidence that the therapeutic administration of potassium chloride caused any amelioration of mental symptoms. However, this lack of correlation probably means little, as it is doubtful whether serum-potassium levels reflect to any true degree variations in intracellular potassium content; nor perhaps in the presence of adrenal disease is it to be expected that the administration of potassium, although causing a rise in serum concentration, can correct a deficiency which is basically intracellular. In our experience, the administration of potassium chloride to patients with psychosis resulting from corticotropin and cortisone is similarly without effect. Therefore, until a satisfactory method has been evolved by which intracellular potassium levels may be accurately computed, this matter must remain *sub judice*.

It will be recalled that in six of the nine cases in the series in which an examination of the spinal fluid was made, an increased total-protein content was discovered,

25. (*a*) Hoagland, H.: In Life Stress and Bodily Disease, Baltimore, Williams & Wilkins Company, 1950, Chap. 21, p. 326. (*b*) Hoagland, H., and Pincus, G.: Proceedings of First Clinical ACTH Conference, Toronto, The Blakiston Company, 1950, p. 544.

26. Hoagland, H.: Psychosom. Med. **12**:142, 1950.

and that in two cases in which the investigation was repeated after operation, the protein content of the spinal fluid was found to have fallen to normal, or near-normal, limits. The significance of this observation is uncertain, nor is there any evidence as yet that the abnormality bears any specific relation to mental disorder. This finding, however, suggests that here, again, is evidence of disordered function within the central nervous system, though the raised protein concentration may result from alteration in permeability of the blood-brain barrier, rather than directly from some metabolic deviation. The occurrence of an increase in the protein content of the spinal fluid brings to mind a similar state of affairs which occurs in myxedema, another endocrine disorder frequently associated with mental disturbance. In this condition there is also a fall in protein content as recovery takes place and the metabolic rate rises.[27] Another, less remarkable possibility is the connection with diabetes mellitus, in some cases of which an increased spinal-fluid protein also occurs.[8]

Last, but not least, are the reactive psychological factors. First, as has already been observed, Cushing's syndrome is a condition which, because of the hirsutism, the obesity, particularly affecting the face, and the changes in the skin, resulting in plethora, marmoration, and acneiform lesions, may cause extreme disfigurement. These are likely to be felt especially keenly by young women, the class of patients most prone to have this disease. Second, the bone changes, particularly osteoporosis of the spine, which, combined with slight trauma, may result in compression and collapse of one or more vertebral bodies, may, and frequently do, give rise to a severe disabling backache and other considerable discomfort. Third, the muscular weakness and fatigue which are an almost invariable, and often severe, accompaniment of the illness, may restrict social and everyday activities. When these factors, combined with others, such as loss of libido, headaches, and dizziness, are taken into account, it is hardly surprising that some degree of depression, despondency, or discouragement occurs in many of the unfortunate sufferers from this disease. One example of this reactive depression to physical changes will suffice to illustrate the point. M. A. (Case 4) was one of several patients who were greatly upset by the alterations in their appearance. While in the hospital she would frequently withdraw to the privacy of her room to escape the gaze of passers-by. How she felt can be understood from the bare statement in her record to the effect that in seven years her appearance had been transformed by her condition from that of an attractive girl to that of an obese and bearded old lady.

CONCLUSIONS

Finally, we wish to attempt to combine in the form of a working hypothesis some of the more important elements of the problems which have been outlined and discussed in this paper. Until many further observations have been collected, and much more detailed study has been carried out on this somewhat amorphous mass of material, formulation is necessarily inexact and incomplete. That we have attempted it at all is due to the belief that in so doing further clarification of the patently

27. Thompson, W. O., and Thompson, P. K.: J. Clin. Invest. **6**:347, 1928. Thompson, W. O.; Thompson, P. K.; Silvers, A. B., and Dailey, M. E.: The Cerebrospinal Fluid in Myxedema, Arch. Int. Med. **44**:368, 1929.

complicated relation between endocrine dysfunction and mental disorder will be achieved.

In all hypotheses there must be an initial assumption, and the present one, which is no exception to the rule, is based on the belief that Cushing's syndrome is one possible result of exposure to nonspecific stress exerted on a person in some as yet unknown way. The foundations for this belief have been laid by Selye and his associates, who have established the relation of nonspecific stress and nervous and psychic phenomena to primary and secondary activation of the pituitary-adrenal system.[28] True, it is difficult to perceive the nature of the stress, if any, to which some of the patients presented may have been subjected; and to suggest, for example, that pregnancy, among other possibly significant happenings, can be considered as a stressful occurrence may seem to some rather far-fetched. However, what can and cannot be considered as a stress must be viewed in relation to the subject. In patients in whom a strong latent predisposition exists to a disease determined by factors which are as yet largely unknown, stressful precipitating occurrences may be slight, and probably in some cases so apparently insignificant as to escape notice.

Therefore, of the many possibilities which can result from the interaction of external environmental stresses and a person of certain predetermined disposition, chronic adrenal hyperfunction may well be one. That which produces the endocrine dysfunction may also cause the neuropsychiatric disorder, or either of these disturbances may be a consequence of the other. Furthermore, it is likely that as a result of the same, or similar, interactions, either endocrine disease or mental illness may, and commonly does, occur alone, for, as has been seen in many of the cases under discussion, mental disorder is by no means an invariable associate of Cushing's syndrome. Conversely, the work of others [29] has revealed evidence of endocrine abnormalities in the schizoaffection reaction, which is at present considered to be a primary mental disorder.

Once the endocrine dysfunction has become established, metabolic abnormalities arise which may cause secondary impairment of cerebral function, and possibly in some cases actual cerebral lesions. Either of these may result in mental disturbance, and in the second instance possibly prevent complete recovery from this. Similarly, physical symptoms appear which may themselves give rise to psychological difficulties of a reactive kind; the latter, in their turn, may, in common with mental symptoms of metabolic or other origin, add to or exacerbate the stress under which the person already labors.

SUMMARY

The neuropsychiatric abnormalities observed in a series of 25 cases of Cushing's syndrome are described.

The significance of these findings, together with those of a number of other authors, is discussed, and a comparison is drawn between these abnormalities and those which sometimes occur as a complication of treatment with corticotropin and cortisone.

28. Selye, H.: J. Clin. Endocrinol. **6**:117, 1946. Selye, H., and Fortier, C.: Psychosom. Med. **12**:149, 1950.

29. Voss, G.: Ztschr. f. d. ges. Neurol. u. Psychiat. **165**:458, 1939. Altschule.[16a] Hoagland and Pincus.[25b]

Emphasis is laid on the fact that, although mental disturbance may be severe, recovery from this, as well as from physical disabilities, is to be expected in a reasonable proportion of cases as a result of adequate surgery, which, it would seem, is the treatment of choice. Three of the four most severely disturbed patients in this series recovered as a result of such treatment.

The fall in the increased protein content of the cerebrospinal fluid after operation, which has also been observed, is thought to be a further indication of the reversibility of the abnormal cerebral function.

In certain cases full recovery may be delayed or prevented, owing to hypoadrenalism following operation, which may later be controlled, or possibly as a result of grosser or irreversible cerebral damage.

In addition, some possibly significant etiological factors are described, and an effort is made to relate these to the occurrence both of endocrine dysfunction and of mental symptoms.

RELATIVE EFFECTS OF OCCIPITAL AND PERIPHERAL BLINDNESS UPON INTELLECTUAL FUNCTIONS

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THE PROBLEM

LASHLEY [1] has shown that the occipital cortex of the rat possesses important extravisual functions in the learning of the maze. One would expect that in man this cortical area would likewise have significant cortical functions, independent of its role as the primary visual center. Particularly in the intellectual areas should the contributions of the occipital cortex be evident. In our well-standardized intelligence tests we have effective instruments for measuring the extent of these contributions in the normal human subject. However, either reliable test information prior to brain injury has not been available or the disturbance has been so severe that extrapolation to normal intellectual function has not been possible.

Even if desirable cases were available, the question arises whether the intelligence tests in ordinary use in clinical work are sensitive enough to measure any loss in intellectual capacity resulting from damage to the occipital cortex. A test like the Wechsler-Bellevue Intelligence Scale, which utilizes a variety of test situations and is widely used clinically, might be an effective instrument in measuring the deteriorative effects of occipital injury. A number of studies with this test have demonstrated its usefulness in detecting mental deterioration as a result of brain damage. Even small lesions of the brain have been detected with this method. For a cortical lesion to be large enough to cause bilateral blindness it must be extensive and must cover most of the total occipital area (according to Krieg,[2] one-tenth of the neurons of the entire cortex are in the visual receptive area). Further, as with other brain injuries, occipital lesions will probably have a differential effect upon the various intellectual operations tested by the Wechsler-Bellevue Scale.

EXPERIMENTAL PROCEDURE

The present experiment was set up to compare the performance of three groups of patients who had been blinded during World War II. One group had lost their sight by direct injury to the eyes, while the second group had intact eyes but had become blind as a result of a brain injury involving the occipital cortex. The precise limits of these injuries to the brain were not known, and they probably involved other cortical and subcortical areas. But in each case the

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Lashley, K. S.: Studies of Cerebral Function Learning: XII. Loss of the Maze Habit After Occipital Lesions in Blind Rats, J. Comp. Neurol. **79**:431-462, 1943.

2. Krieg, W. J. S.: Functional Neuroanatomy, Philadelphia, The Blakiston Company, 1942.

locus of penetration of the skull was the occipital pole. All members of the group with peripheral injuries (P group) were totally blind, whereas those of the group with occipital lesions (O group) had some residual sight because of macular sparing. To serve as a control a third group of subjects was added, peripherally blinded and with an injury to an area of the brain other than the occipital (N group).

The members of all three experimental groups had been given the Army General Classification Test before they were blinded, when they first entered the Army. This test consisted of three subtests: Vocabulary, Arithmetic, and Block Counting. Subsequent to being blinded, each subject was given the Wechsler-Bellevue Intelligence Test, verbal scale, which consists of six subtests: Information, Comprehension, Digit Span, Arithmetic, Similarities, and Vocabulary tests. In an earlier paper I [3] reported the test finding on 624 of these blinded soldiers. The results indicated that blindness alone, when it occurs in adult life, does not appear to affect intellectual functions as measured by this test. No essential differences could be found between this blinded group and other, nonblinded veterans except for a somewhat lower Digit-Span score, which was attributed to decreased attentivity.

In this study a direct comparison of scores on the Army General Classification Test and the Wechsler-Bellevue Intelligence Test was not possible because the Wechsler-Bellevue total score is weighted, whereas the Army General Classification score is a standard one. But the subtest scores of the Wechsler-Bellevue Scale are standard scores, with a mean of 10 and a standard deviation of 3; the Army General Classification mean is 100, and the standard deviation is 20. In order to make means and standard deviations of the Wechsler-Bellevue subtests comparable with those of the Army General Classification Test, each of the six Wechsler-Bellevue subtests was taken independently and the individual scores were equated with the scores for the Army General Classification Test by means of a conversion table. Each subtest mean of 10 was converted to 100, and the standard deviation of 3, to 20. Thus, each subtest unit above or below the mean of 10 was multiplied by 6.67 and added to or subtracted from 100 to obtain the equivalent Army General Classification score. For example, a subtest score of 13 became 120 as an Army General Classification equivalent; a score of 8 became 86.67. The range was 53.33 to 153.33.

The differences between each subject's equivalent subtest score and his Army General Classification score were then tabulated, and a mean difference was calculated. The significance of the individual differences was determined by the usual small-sample formula for the significance of the difference between related means. Each Wechsler-Bellevue subtest was thus compared independently with the Army General Classification Test.

RESULTS

The results are tabulated in the accompanying table. In the last column are the average scores for the total sample of 407 blinded soldiers. It can be seen that performance on each of the Wechsler-Bellevue subtests following blindness, except, the Digit Span, is higher than the earlier Army General Classification score. The 118 subjects of the P group obtained mean scores on all tests very similar to the mean score for the total sample; postblindness scores were again above those for the preblindness Army General Classification Test in all Wechsler subtests except the Digit Span.

When performances of the O group are compared with those of the P group, several interesting differences are observed. In the Army General Classification Test the O group did considerably better than the P group; the N group's performance was in between. But after being blinded, the O group fell below the P group in four of the six subtests. This postblindness inferiority of the O group assumes

3. Levine, J.: Intelligence Test Scores of Newly Blinded Soldiers, J. Consult. Psychol. **14**:311-315, 1950.

greater significance in view of the preblindness superiority. The N group, on the other hand, retained its higher mean preblindness scores in four of the six subtests after blinding.

The test which probably reflects the greatest difference between the O and the P group is the Arithmetic. The individual Arithmetic scores for the P group are consistently higher than the Army General Classification Scores. The average of the individual differences is statistically significant to the 1% level of confidence. For the O group, the situation is reversed: The individual Arithmetic scores after blindness are below the Army General Classification scores, and the mean of these differences is likewise significant to the 1% level. The scores for the N group again seem to fall somewhere between those for the other two, but tend toward those for the O group. The individual Arithmetic scores tend to be lower than the Army General Classification scores, but the mean difference is not significant.

Average Individual Differences Between Army General Classification Test and Wechsler-Bellevue Scores of Brain-Injured and Non-Brain-Injured Blinded Soldiers

Group	Occipital Injury			Nonoccipital Injury			Peripheral Injury			Blinded, Total Sample
No. Cases	20			32			118			407
AGCT †	Mean 104.0			100.5			93.7			94.4
W-B* Subtest	Mean	Mean Difference W-B and AGCT	P† Value	Mean	Mean Difference W-B and AGCT	P† Value	Mean	Mean Difference W-B and AGCT	P† Value	Mean
Information	101.3	− 2.82	0.60	105.4	+4.95	0.05	103.3	+ 9.63	0.01	104.5
Comprehension	101.3	− 2.82	0.40	108.1	+7.66	0.01	107.5	+13.79	0.01	107.5
Digit span	82.7	−22.47	0.01	91.7	−8.80	0.02	92.0	− 2.74	0.20	93.3
Arithmetic	89.0	−17.08	0.01	98.1	−2.75	0.50	99.8	+ 6.17	0.01	102.7
Similarities	110.3	+ 6.18	0.05	107.9	+7.68	0.01	104.7	+10.94	0.01	106.7
Vocabulary	102.7	− 1.48	0.70	97.2	−3.18	0.10	95.5	+ 2.05	0.20	106.7

* AGCT indicates Army General Classification Test; W-B, the Wechsler-Bellevue Intelligence Test.
† This is the probability that a difference this great or greater could have arisen simply through errors of random sampling.

In all three groups, the Digit Span score was the lowest subtest score, though it was significantly lower than the Army General Classification score in only the O and the N group. The Similarities test showed the greatest consistency for all three groups. Scores in this test were significantly higher. These two findings are strikingly consistent with those of the earlier study of the total sample,[3] in which the Digit Span score was the lowest subtest score and the Similarities score nearly the highest. The lower Digit Span scores were interpreted in that paper[3] as reflecting an impairment of attention because of anxiety resulting from Army experiences, especially the loss of sight.

COMMENT

The conclusions which are drawn from the present study must be tempered by the recognition of two important uncontrollable shortcomings. The first is the obvious fact that two separate, though similar, intelligence tests were used as a basis of comparison of the effects of occipital-lobe injury. The two tests were standardized on two different samples, although in terms of age, education, and social status the two appear comparable. Of greater importance is the fact that the extent of the lesions in any of the brain-injured patients is not known. In the

case of the occipital group, for instance, we do not know how much of the peristriate and subcortical areas was involved in the injury. We can assume that on the whole the amount of brain damage in the occipital group is larger than in the nonoccipital group, since even minimal lesions were included in the latter. The failure of the N group to show as much mental deterioration as the O group may therefore have been due to less cortical damage.

Notwithstanding the foregoing limitations, the present findings indicate that, in addition to serving as the primary cortical center for vision, the occipital cortex of man performs important intellectual functions. In this respect, they confirm the findings of Lashley with the rat. They also tend to support his hypothesis that the occipital cortex possesses functions of a nonvisual nature, which it performs in common with the other cortical areas. The inference may be drawn that cortical tissue possesses nonlocalized integrative properties which characterize behavior in general but which are particularly evident in the so-called higher mental processes. The clinical findings of other investigators with the Wechsler-Bellevue Intelligence Test tend to support such a conclusion. These studies have shown that, regardless of the locus of the brain lesion, certain test situations of the Wechsler-Bellevue Scale consistently reveal signs of mental deterioration, whereas other subtests are less vulnerable. Wechsler [4] found that Vocabulary, Information, and Comprehension scores were least affected by brain injury, whereas Digit Span and Digit Symbol scores were most affected. On the basis of his study of intellectual impairment following head injuries, Ruesch [5] concluded that certain general functions were most severely affected, namely, speed, judgment, and ability to sustain effort. According to Ruesch, "the impairment seems to be related to the severity of the brain damage," and not to the locus. Schilder,[6] Benton and Howell,[7] and Conkey [8] independently concluded that a generalized defect was observable in their cases of brain injury. Since 1881, when Goltz [9] emphasized the significance of attention as the important general function most clearly affected by brain damage, investigators have continually hypothesized general cortical properties common to all areas. Lashley [1] has made these notions most explicit and acceptable experimentally. The present study, in conjunction with the other clinical evidence, clearly supports such a hypothesis.

In the present study, the test situations which show the greatest drop in score in the group with occipital lesions seem to be those which are most dependent upon speed of thinking and sustained attention. These are the Arithmetic and Digit Span tests. The fact that the O group showed impairment in the ability to solve relatively simple arithmetical problems that have short time limits may indicate a specific loss

4. Wechsler, D.: Measurement of Adult Intelligence, Ed. 3, Baltimore, Williams & Wilkins Company, 1944.

5. Ruesch, J.: Intellectual Impairment in Head Injuries, Am. J. Psychiat. **100**:480-496, 1944.

6. Schilder, P.: Psychic Disturbances After Head Injuries, Am. J. Psychiat. **91**:155-188, 1934.

7. Benton, A. L., and Howell, I. L.: The Use of Psychological Tests in the Evaluation of Intellectual Function Following Head Injury: Report of a Case of Post-Traumatic Personality Disorder, Psychosom. Med. **3**:138-151, 1941.

8. Conkey, R. C.: Psychological Changes Associated with Head Injuries, Arch. Psychol. **232**:1-62, 1938.

9. Goltz, F.: Über die Verrichtungen des Grosshirns, Arch. ges. Physiol. **26**:1-49, 1881.

of old-established learned habit patterns. But it appears more likely that the lowered score reflects a reduction in the ability to think rapidly and with concentrated attention. That the Arithmetic score is a genuinely depressed score is further evidenced by the fact that approximately one-third of the Army General Classification Test consists of similar arithmetical problems. The lowered Digit Span score supports this inference, since, to some extent at least, this test measures similar functions.[10]

It is interesting that those intelligence test situations which were least affected by brain injury in this study, as well as in other studies, are just those which involved the abstract thinking emphasized by Goldstein.[11] Thus, Wechsler [4] and Allen [10a] found that the Information, Comprehension, Vocabulary, and Similarities subtests were least affected. The Similarities subtest would appear to be the one most clearly to characterize abstract thinking. In the present study, this subtest showed the least, if any, effect of brain damage. The explanation may lie in the fact that the scoring of these subtests is not sufficiently sensitive to pick up the impairment in abstract thinking produced by such lesions.

CONCLUSIONS

The intelligence test scores of three groups of blinded soldiers were compared before and after blinding. The three groups comprised (*a*) veterans who were blinded as a result of an injury to the occipital cortex; (*b*) veterans who were blinded by direct damage to their eyes, and (*c*) veterans who were blinded by direct damage to their eyes but who also had injuries involving areas of the brain other than the occipital cortex. Scores on each of the six tubtests on the Wechsler-Bellevue Intelligence test, verbal scale, were compared with scores on the Army General Classification Test, which was taken by each subject prior to blindness, upon entrance into the Army.

The results indicated that occipitally blinded subjects showed impairment of intellectual functions after the brain injury. The blinded group with lesions in areas other than the occipital lobe also showed impairment of mental function, but not as great as the group with occipital injuries. This difference was interpreted as resulting from a difference in the amount of cortical tissue destroyed in the two groups.

The most striking loss occurred in the Arithmetic score; this loss was interpreted as due to general impairment of capacity to perform mental operations with speed and with sustained attention. In general, the findings were considered to support Lashley's hypothesis that the occipital cortex, in common with other cortical areas, performs intellectual functions of a nonvisual nature. Certain uncontrollable factors, such as ignorance of the extent of the brain lesions, reduce the validity of this study.

10. (*a*) Allen, R. M.: The Test Performance of the Brain Injured, J. Clin. Psychol. **3**:225-230, 1947. (*b*) Rapaport, D.; Gill, M., and Schafer, R.: Diagnostic Psychological Testing: The Theory, Statistical Evaluation, and Diagnostic Application of a Battery of Tests, The Menninger Clinic Monograph Series No. 3, Chicago, The Year Book Publishers, Inc., 1945, Vol. I.

11. Goldstein, K.: After-Effects of Brain Injuries in War: Their Evaluation and Treatment, New York, Grune & Stratton, Inc., 1942.

EFFECTIVENESS OF CHORDOTOMY IN PHANTOM PAIN AFTER AMPUTATION

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NO FORM of post-traumatic neuralgia causes greater distress to its victims, or is more difficult to relieve, than the painful phantom of an amputated limb. Ten years ago Bailey and Moersch,[1] after summarizing the experience at the Mayo Clinic, found that no form of surgical intervention was effective. They concluded that the disagreeable postural illusions and painful sensations must originate at supraspinal levels and that their "origin is central (that is, intracranial) and most probably psychic." This opinion is still frequently cited, and the general consensus is that anterolateral chordotomy generally fails to relieve the painful phantom of the amputee (Browder and Gallagher[2]; Horrax[3]). Riddoch,[4] who wrote one of the best descriptions of this condition, was not so pessimistic and stated that "when . . . pain in the phantom is successfully abolished by lateral cordotomy . . ., the phantom may behave as if it has been painless from the first." In our experience with 14 cases in which the pain was so severe that surgical relief became imperative to prevent narcotic addiction, painful sensations in the amputated foot or hand were abolished in 11 and failed to reappear as long as total insensibility to ordinary painful stimuli (analgesia) persisted.

Our recent evaluation of 241 anterolateral chordotomies, published in collaboration with Hawkins and Nilges,[5] has shown that to achieve and maintain complete and permanent analgesia, radical transection of the contralateral anterior quadrant of the cord is necessary. The level of transection must be well above the highest inflow of the primary sensory axons, as the secondary axons may require a larger number of segments for the decussation than is generally supposed (White, Sweet, Hawkins, and Nilges[5]). To be successful the level must be established at operation

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Read at the Seventy-Sixth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 19, 1951.

1. Bailey, A. A., and Moersch, F. P.: Phantom Limb, Canad. M. A. J. **45**:37-42 (July) 1941.

2. Browder, E. J., and Gallagher, J. P.: Dorsal Cordotomy for Painful Phantom Limb, Ann. Surg. **128**:456-469 (Sept.) 1948.

3. Horrax, G., in discussion on Browder and Gallagher.[2]

4. Riddoch, G.: Phantom Limbs and Body Shape, Brain **64**:197-222 (Dec.) 1941.

5. White, J. C.; Sweet, W. H.; Hawkins, R., and Nilges, R. G.: Anterolateral Cordotomy: Results, Complications and Causes of Failure, Brain **73**:346-367 (Sept.) 1950.

on the conscious patient, with the use of local anesthesia,[6] and analgesia must remain so complete that the patient never regains the ability to discriminate between a blunt and a sharp point by any difference in sensation whatever. The surgical technique and methods of testing employed by many neurosurgeons do not measure up to these standards, and their results have been unsatisfactory. This applies as well to relief of pain in malignant disease, tabetic crises, and many other benign conditions.

As a result of inability to achieve more consistent satisfactory results in many varieties of severe persistent pain by anterolateral chordotomy, numerous authors have recently advocated the substitution of bilateral frontal leucotomy (Freeman and Watts[7]; Hawkes and Gotten[8]; Hamilton and Hayes[9]; Kolb[10]). Leucotomy is a far easier technical procedure for the surgeon; but because of the severe mental and psychical deterioration that so often ensues, we feel that it is never justified except as a last resort. We are willing to recommend leucotomy only when pain is situated at too high a level to be controlled by section of the spinothalamic tract in the cord or medulla, or after a properly executed chordotomy has been tried and failed (White[11]).

There should be no difficulty in convincing members of the medical profession that specific interruption of pain-conducting axons within the spinal cord is preferable to cutting the frontothalamic connections, provided it can be shown that the more conservative operation is followed by a gratifying proportion of successful results without serious complications. Our experience with 10 cases of painful phantom of the amputated lower extremity, summarized in Table 1, leaves little question on either score. There have been no deaths in this series (or in 32 additional chordotomies performed for other nonmalignant neuralgias). There has also been no serious motor weakness—a potential complication especially to be feared, since it would involve the sound limb. Seventy per cent of patients have been relieved of all pain connected with the phantom, and in 3 of these patients awareness of the phantom has disappeared as well. These patients have been followed over periods ranging from 18 months to 3 years.

The three failures deserve special consideration. Lack of success in Case 10 was due to our inability to obtain an adequate extent of analgesia. In Case 4 the patient was completely relieved at first, but pain returned with the reappearance of islands of hypalgesia in the stump, which gave rise to paresthesia on rapid pricking with a pin. Persistence of the painful phantom in Case 7 was the only instance in which an apparent complete severance of pain pathways below the midthoracic level failed to relieve a sensation of heat in the phantom foot and disagreeable paresthesias

6. Local anesthesia can, however, be supplemented with light thiopental-sodium and nitrous-oxide anesthesia, the patient being allowed to awaken for testing and then again put to sleep. With patience on the part of the surgeon and occasional resort to pentylenetetrazol U. S. P. (metrazol®), adequate sensory testing can be carried out with a minimum of discomfort.

7. Freeman, W., and Watts, J. W.: Pain Mechanisms and the Frontal Lobes: A Study of Prefrontal Lobotomy for Intractable Pain, Ann. Int. Med. **28**:747-754 (April) 1948.

8. Hawkes, C. D., and Gotten, N.: Pre-Frontal Lobotomy Vs. Cordotomy for Relief of Intractable Pain, Tr. Am. Neurol. A. **73**:208-210, 1948.

9. Hamilton, F. E., and Hayes, G. J.: Prefrontal Lobotomy in the Management of Intractable Pain, Arch. Surg. **58**:731-738 (June) 1949.

10. Kolb, L.: Psychiatric Aspects of Treatment for Intractable Pain in the Phantom Limb, M. Clin. North America **34**:1029-1041 (July) 1950.

11. White, J. C.: Frontal Leucotomy Versus Cordotomy for Relief of Pain, Surg., Gynec. & Obst. **92**:469-480 (April) 1951.

in the pelvic stump. In this case, with recurrent pelvic chondrosarcoma, it is possible that secondary pain-conducting axons had escaped destruction, as one cannot test for the presence of sensory connections from a missing extremity.

There were postoperative complications in three cases. Partial retention of urine in Case 6 was relieved by transurethral resection of the hypertrophied prostate. Slight residual weakness of the leg on the side of the cord incision was the cause of mild complaints by the patient in Case 9, a woman with a leg already weakened by

TABLE 1.—*Relief of Phantom Pain After Amputation of the Lower Limb*

Case	Age, Yr.	Condition	Level of Chordotomy	Level of Analgesia	Result
1 C. W.	70	Phantom foot 18 yr. after thigh amputation; two previous unsuccessful resections of neuromas	T2	...	Patient comfortable at 2½ yr., although he noticed occasional sensations in phantom great toe
2 A. N.	61	Crushing sensations in phantom ankle for 2 mo. after hip disarticulation for sarcoma	T2	T7	Free of pain at 27 mo., but aware of mild sense of stiffness in foot and big toe
3 H. A.	51	Pinching and burning pain in phantom foot 7 mo. after hip disarticulation	T2	T9	Complete loss of pain, as well as of awareness of phantom, at 8 mo.
4 M. D.	40	Pain in phantom leg and stump after thigh amputation	T2	T5	Pain-free stump with loss of phantom for 8 mo., with gradual return to former severity at 2 yr.
			C7	T5	Again free of pain for 9 mo., with recurrent pain observed coincident with appearance of islands of hypalgesia
5 A. D.	73	Pain in phantom foot and in below-knee amputation stump for 17 yr.	T3	T5	All phantom pain relieved, but patient complained of residual burning in stump and annoyance from cutaneous analgesia
6 J. D.	66	Diabetes with midthigh amputation; cramps in sole and pain persisting in phantom big toe after 2 yr.	T3	T10	Free of all pain, as well as phantom sensations, at 4½ yr.
7 F. I.	51	Pain in stump and burning in phantom foot 18 mo. after hip disarticulation; recurrent chondrosarcoma of acetabulum	T2	T7	Total failure; no improvement after posterior chordotomy (column of Goll); amelioration following bilateral frontal leucotomy
8 N. B.	42	Previous lumbar sympathectomy and midthigh amputation of right leg in 1942 for Buerger's disease; phantom foot projected from stump with toes contracted	T2	T8	Lasting relief of phantom pain at 13 mo., but recurrence of local stump neuralgia in an island of hypalgesia
			T3	T10	Relieved by secondary chordotomy
9 J. B.	37	Gritti-Stokes amputation necessitated by old poliomyelitis and infection, followed for 3 yr. by neuralgia in stump and painful phantom	T3	T8	Free of all pain and awareness of phantom at 2½ yr.
10 W. S.	60	Bilateral traumatic thigh amputation; at 5½ yr. patient complained that phantom feet were painfully contracted; paranoid psychosis and morphine addiction	T2 (left)	T8	Recurrence at 1 mo. with islands of hypalgesia in stump
			T1-T3 (bilateral)	Incomplete	Early recurrence at 1 mo. with islands of hypalgesia in both stumps
			C4 (left)	Incomplete	High-grade hypalgesia to T7, without relief; effective relief after bilateral frontal leucotomy, but mental deterioration required institutional care

poliomyelitis. A disagreeable rare side-effect of chordotomy occurred in Case 5, as the patient, in whom all phantom sensation and pain had disappeared, acquired a burning sensation in his stump and a neurotic fixation on the fact that he could pass a needle through the analgesic skin without any feeling of pain.

In summary, it is evident that, with rare exceptions, it is possible to relieve the painful quality of a phantom lower extremity, and often all awareness of the phantom as well, by a properly executed anterolateral chordotomy.

With amputations of the upper extremity the problem is much more difficult, as it is not an easy matter either to achieve or to maintain analgesia over the entire

distribution of the brachial plexus. Yet Falconer and Lindsay,[12] in New Zealand, have reported success in two patients followed for 12 and 6 months, respectively. Our experiences in four cases are summarized in Table 2. In Case 12 there was immediate lack of success despite an apparently adequate level, and in Cases 11 and 13, ultimate recurrence of pain after three years and six months, respectively, as the level of analgesia ultimately fell. In Case 14 recent follow-up information shows that there has been no return of pain in 18 months. It is quite impossible to explain the mechanism of late falls in the level of analgesia and its replacement by hypalgesia. From our experience with a large series of chordotomized patients, it is clear that the original pain often, although not invariably, will return if there is recovery of even small patches of hypalgesia (when the point of a pin projecting beyond the finger tip is not necessarily felt as sharp, but is perceived as different from the pressure of the finger tip alone). In cases of this sort a few pain-conducting axons must remain intact, and a more radical transection of the anterolateral

TABLE 2.—*Relief of Phantom Pain After Amputation of Upper Limb*

Case	Age, Yr.	Condition	Level of Chordotomy	Level of Analgesia	Result
11 P. J.	44	Traumatic amputation of upper humerus with infection; multiple operations for drainage; resection of neuromas, and brachial plexectomy	Medulla below obex	C3	Freedom from all painful and phantom sensation for 3 yr.; gradual recurrence to complete return of pain at 5 yr.
12 R. S.	53	Traumatic amputation of forearm, with fingers painfully contracted; postcentral resection of sensory cortex, without benefit	C2	C3	Analgesia apparently complete at 9 mo., but painful fingers still project from stump
13 M. M.	48	Scapulohumeral disarticulation for chondrosarcoma, with contracted phantom arm and hand; anterior and posterior rhizotomy and postcentral corticectomy	C1	C3	Relief for 6 mo.; then recurrence with hypalgesia and reference of sensory stimuli in lower part of body to stump
14 J. W.	52	Traumatic midhumeral amputation, with painful cramping in phantom hand	C1	C5	Patient free from symptoms and working steadily at 18 mo.

column will usually relieve the sufferer again. We have hesitated to attempt this in our high cervical chordotomies but have done so with success in an amputee with pain limited to the stump. Unfortunately, in this series, the secondary chordotomy in Case 4 was a failure, for the sensory level had again fallen at nine months.

In Case 10 an attempt was made to sever the pain pathways completely on each side. In spite of every effort, we found it impossible to produce a complete and enduring analgesia. At each operation the patient, fully conscious, was tested carefully on the table and a satisfactory sensory level obtained, only to have analgesia replaced by hypalgesia, with return of the painful phantom within a month. As this man was addicted to alcohol, as well as morphine, and was also developing paranoid traits, bilateral frontal leucotomy was finally performed. He was freed of his pain and drug addiction, but at the cost of such severe mental deterioration that he had to be committed to a state hospital for the seven ensuing months. At the end of this period his psychological status has definitely improved, and it is hoped that he will soon be able to return to his home.

12. Falconer, M. A., and Lindsay, J. S. B.: Painful Phantom Limb Treated by High Cervical Chordotomy: Report of 2 Cases, Brit. J. Surg. **33**:301-306 (April) 1946.

COMMENT

We have taken care to record our difficulties in detail in order to assess the value of chordotomy in this admittedly difficult problem of phantom pain. It is clear that this pain is abolished in a high proportion of cases as long as analgesia is complete. Under these circumstances, the phantom remained painful only in Case 7 in the lower extremity and in Case 12 in the upper extremity. We were unable to produce an adequate degree of analgesia in Case 10 or to maintain it permanently in Cases 4, 11, and 13, amputations being at the shoulder level in the last two cases.

Other varieties of surgical intervention, aside from operations on the frontal lobes, have failed in a far higher proportion of cases. Resection of end-bulb neuromas of the severed nerves in the stump or reamputation is never successful (Livingston [13]). Ellonen,[14] in Finland, reported a number of favorable results following lumbar sympathetic block or sympathetic ganglionectomy, but his compatriot Kallio,[15] who followed a larger series of patients for longer periods, found that lasting improvement was extremely rare. Echlin [16] reported a single successful result following lumbar sympathetic ganglionectomy, in which he was able to reproduce the painful symptoms on stimulating the lumbar chain, with the use of local anesthesia. This case is well documented, with many months' observation; yet in stimulating the lumbar ganglia in five conscious subjects and the upper thoracic ganglia in three others, we were never able to elicit pain referred to the foot or hand, and could elicit it to the upper arm only once. While sympathectomy in our hands [17] has often given effective relief from persistent pain located in the stump following toe or finger amputations (when the neuralgia was associated with cold, cyanotic extremities and was temporarily relieved by sympathetic block), we doubt whether this operation has much to offer in the case of amputations above the ankle or wrist. A most instructive wartime experience was reported by Woodhall,[18] in which a soldier suffered from both a disagreeable cramping phantom of his hand and causalgic burning pain in the forearm stump. After thoracic sympathectomy, the causalgic syndrome disappeared, but the phantom remained unchanged. In addition to this observation, a case was reported by Echols and Colclough [19] in which a painful phantom developed after amputation of the leg for progressive arterial occlusion after a previous sympathetic denervation.

Posterior chordotomy to interrupt postural sensations ascending in the dorsal columns has been advocated by Pool [20] and by Browder and Gallagher.[2] In only one of Pool's three cases was relief satisfactory after a brief period of observation, and

13. Livingston, K. E.: The Phantom Limb Syndrome: A Discussion of the Role of Major Peripheral Nerve Neuromas, J. Neurosurg. **2**:251-255 (May) 1945.

14. Ellonen, A.: L'effet de la sympathectomie sur le fantôme douloureux d'un amputé, Acta chir. scandinav. **93**:131-145, 1946.

15. Kallio, K. E.: Permanency of the Results Obtained by Sympathetic Surgery in the Treatment of Phantom Pain, Acta orthop. scandinav. **19**:391, 1950.

16. Echlin, F.: Pain Responses on Stimulation of the Lumbar Sympathetic Chain Under Local Anesthesia: Case Report, J. Neurosurg. **6**:530-533 (Nov.) 1949.

17. White, J. C., and Sweet, W. H.: Pain: Its Mechanisms and Neurosurgical Control, Springfield, Ill., Charles C Thomas, Publisher, to be published.

18. Woodhall, B.: Personal communication to the authors.

19. Echols, D. H., and Colclough, J. A.: Abolition of Painful Phantom Foot by Resection of the Sensory Cortex, J. A. M. A. **134**:1476-1477 (Aug. 23) 1947.

20. Pool, J. L.: Posterior Cordotomy for Relief of Phantom Limb Pain, Ann. Surg. **124**: 386-391 (Aug.) 1946.

in a recent letter he states that he has lost his enthusiasm for this procedure. In the six cases reported by Browder and Gallagher, the relief of pain and abnormal postural sensations was encouraging in the lower extremity but "not so good" in the upper. Browder,[21] however, remains an advocate of this procedure when the primary complaint consists of distorted sensations of the body image rather than severe pain. In three cases in which the latter was the predominant complaint, he has obtained satisfactory relief, although the phantom has persisted in a painless form. In our single section of Goll's column in Case 7 there was no noticeable change in the symptoms.

Resection of the postcentral convolution (cortical Areas 1 to 3 of Brodmann) theoretically should remove the higher centers where sensation of body posture is integrated. It is questionable, however, whether a sufficient extent of sensory cortex can be resected. The dramatic case reported by Head and Holmes,[22] in which all awareness of a painful phantom was abolished after thrombosis of the middle cerebral artery, led de Gutiérrez-Mahoney [23] to try postcentral corticectomy. Results in his four cases, and in another (Echols and Colclough [19]), after brief observation, were promising, but later inquiries have revealed that pain has frequently returned. In the cases reported by Lhermitte and Puech [24] and by Horrax [25] there was no benefit. This operation had been performed by other surgeons in Cases 12 and 13 of our series, but with only transitory improvement and complicating epileptic seizures. We regard it as a useless and dangerous procedure.

This leaves for further consideration only the operations on the frontal lobes. We have had no personal experience with topectomy, the limited resection of Areas 9 and 10, advocated by Pool.[26] The relatively nonmutilating unilateral frontal leucotomy of Scarff [27] has given us very satisfactory results in a series of patients with malignant disease whose death occurred within six months of operation. On the other hand, when survival exceeded this period, pain has usually returned. This procedure cannot, therefore, be recommended for the postamputation neuralgias. After secondary leucotomy of the other frontal lobe, or bilateral primary leucotomy, psychical deterioration has invariably been severe. While mental confusion, loss of initiative and affect, childishness, and socially intolerable behavior may often be of relatively brief duration, these handicaps sometimes persist for months. This is illustrated by the case reported by Kolb.[10] Here, the suffering caused by a lower-limb phantom had been relieved, but at the expense of socially acceptable behavior and with much mental retardation. One might well ask whether this sacrifice was justifiable without a preliminary trial of chordotomy. Although Kolb's patient

21. Browder, J.: Personal communication to the authors.

22. Head, H., and Holmes, G.: Sensory Disturbances from Cerebral Lesions, Brain **34**:102-254, 1911.

23. de Gutiérrez-Mahoney, C. G.: Treatment of Painful Phantom Limb by Removal of Post-Central Cortex, J. Neurosurg. **1**:156-162 (March) 1944.

24. Lhermitte, J., and Puech, P.: L'algo-hallucinose des amputés: Traitement par le résection du névrome, l'infiltration de la chaîne sympathique, une double myélotomie postérieure, la résection du lobule pariétal supérieur, Rev. neurol. **78**:33-35 (Jan.-Feb.) 1946.

25. Horrax, G.: Experiences with Cortical Excisions for the Relief of Intractable Pain in the Extremities, Surgery **20**:593-602 (Nov.) 1946.

26. Pool, J. L.: Topectomy: A Surgical Procedure for the Treatment of Mental Illnesses, A. M. A. Arch. Neurol. & Psychiat. **65**:105-106 (Jan.) 1951.

27. Scarff, J. E.: Unilateral Prefrontal Lobotomy for the Relief of Intractable Pain: Report of 58 Cases with Special Consideration of Failures, J. Neurosurg. **7**:330-336 (July) 1950.

required frequent doses of pantapon* (a mixture of the hydrochlorides of the opium alkaloids) for control of his pain, he appears to have been no more dependent on narcotics than a number of our patients who responded extremely well to anterolateral chordotomy.

In our two cases in which chordotomy had failed despite every effort, leucotomy was finally resorted to because unremitting pain and drug addiction had made life intolerable both to the patient and to his family. The following brief reports will suffice to illustrate the good and the bad sequelae of these operations:

CASE 7.—A man aged 51 continued to complain of painful contractions in his phantom thigh muscles after disarticulation of the hip for chrondrosarcoma of the right femur, with local recurrence in the acetabulum. He also said that it felt as though his foot were pressed against a hot plate. The painful phantom persisted after two successive sections of the left spinothalamic tract, with a level of complete analgesia to the seventh thoracic segment. Subsequent section of the fasciculus gracilis and the anterior column on the right side likewise failed. This operation resulted in a definite reduction of touch and figure perception on the right side of the abdomen and the right groin and buttock. Vibratory sense was likewise abolished to the lower costal margin. The level of analgesia remained at the seventh thoracic dermatome on the right, but the sensation of pinprick was also eliminated below the first sacral dermatome on the left. The latter, however, was soon recovered. Final relief was achieved by bilateral frontal leucotomy. After this operation he was at first disoriented and confused, but his conduct, although childish, was not objectionable. After his return home, his wife, an intelligent school teacher, reported that he had no disturbing psychical changes as a result of the leucotomy. He was able to enjoy her companionship and that of his friends. He never mentioned the operations or the suffering he had endured, and he did not ask for morphine until new pains developed with the appearance of pulmonary metastases. He then regarded his pain "as a little child would, being very noisy and audible in his suffering," but forgetful about it during remissions. He showed no concern over the obvious manifestations of terminal malignant disease, of which he died in five months.

For this unfortunate person, bilateral leucotomy was a happy solution of the tortures of his fatal disease, but the mental impairment and sacrifice of finer qualities in his personality would have constituted a formidable sacrifice for the ordinary patient with a painful phantom. This is illustrated to a more striking degree by the following case, in which addiction to alcohol, as well as morphine, and added psychotic traits forced us to resort to leucotomy, after three attempts to section the anterolateral columns had failed to secure analgesia.

CASE 10.—Amputation of both thighs, when the patient, a man aged 53, was run over by a train six years before, had resulted in bilateral painful phantom. He developed paranoid traits, as well as addiction to both alcohol and morphine, never left his house, and was subject to violent outbursts of temper. In spite of two unilateral and a bilateral transection of the anterolateral quadrants and a high level of analgesia on testing, islands of hypalgesia invariably appeared, and his painful phantoms returned. As he and his wife insisted on further surgery, a left frontal leucotomy was performed in March, 1950. This produced a transitory period of apathy, during which he did not require morphine, but within a month his pains were again as severe and demoralizing as ever. After transection of the frontal white matter on the right side, just anterior to the tip of the ventricle, mental retardation was severe. He became incontinent of urine and feces and spent his time masturbating and staring blankly at the window or ceiling. This asocial behavior, disorientation, and suspicion of people necessitated his commitment to a state hospital. Now after 10 months, a social worker reports that his personality is greatly improved and that it will be possible to discharge him as soon as he becomes tidier.

In the final evaluation of these two cases, we and all concerned have agreed that leucotomy was justified, but only because every effort had first been made to free the patients of their pain by chordotomy. With evidence that a high proportion of painful phantoms can be relieved by the analgesia that follows a well-performed

transection of the anterolateral spinal quadrant, we submit that this relatively benign operation should always be the procedure of choice, at least with the phantom neuralgias of the lower extremity. In cases in which the arm is involved, especially after amputation at the shoulder level, permanent, sufficiently high analgesia is difficult to obtain. Until the technical difficulties with spinothalamic tractotomy at the upper cervical and medullary levels can be overcome, frontal leucotomy or topectomy may be regarded as justifiable primary procedures in the treatment of painful phantoms in the upper extremity. In order to avoid the psychical mutilation that often follows bilateral operation on the frontal lobes, we shall, nevertheless, persist in the endeavor to perfect the technique of interrupting the secondary pain-conducting axons from the brachial plexus, since we know that if permanent analgesia can be maintained it will be just as effective in the upper as in the lower extremity and will be obtained at but little greater risk.

SUMMARY AND CONCLUSIONS

In past reported experience, anterolateral chordotomy has so often failed to relieve painful phantoms after amputation that many neurosurgeons recommend that it be replaced by frontal leucotomy.

In our own experience with more radical transection of the anterolateral spinal quadrant and the establishment of a high sensory level by testing, with the use of local anesthesia, we have failed to obtain early satisfactory relief in only 3 of 14 cases. Long-standing successful results were obtained in 7 of 10 cases of intervention for painful phantom of the lower extremity. The three failures were due to persistence of painful postural sensations, despite an adequate level of analgesia in Case 7, a late drop in the level in Case 4, and inability to obtain full analgesia in Case 10. Of four cases of painful phantoms in the upper extremity, in which it is exceedingly difficult to obtain permanent analgesia in the upper cervical dermatomes, there were ultimate failures in two cases because of late falls in the analgesic level at six months and three years, respectively, and in one case relief was not obtained, in spite of apparent analgesia extending to the third cervical dermatome. Complications following these chordotomies have not been frequent or serious.

In view of the serious mental and psychical deterioration that so often accompanies sacrifice of portions of the frontal lobes, we recommend that anterolateral chordotomy be selected as the primary operation for every painful phantom of the lower extremity, unless there is advanced narcotic addiction or serious psychoneurotic overlay.

For desperate cases of phantom arm, especially after amputation near the shoulder, in which technical difficulties complicate complete interruption of the secondary axons conducting pain, some form of operation on the frontal lobes may be justified as the preferable procedure.

Results with other surgical procedures, such as excision of neuromas, reamputation, sympathectomy, posterior-column chordotomy, and postcentral resection of sensory cortex, are reviewed and found wanting.

WORD DEAFNESS AND WERNICKE'S APHASIA

Report of Cases and Discussion of the Syndrome

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FROM THE confusing mass of clinical symptoms displayed by patients with disorders of the speech mechanism, neurologists have been fairly well agreed on isolating "sensory aphasia" as a well-defined syndrome. As described by Wernicke,[1] this aphasia, which is now known by his name, consists of loss of comprehension of spoken language and loss of ability to write and read (silently), with power of articulate speech retained but distorted in that words and syllables are misplaced and mispronounced—paraphasia.

Lichtheim[2] first described a different syndrome, in which the inability to understand spoken words was an isolated deficit—unaccompanied by distortion of spontaneous speech or by severe disturbance in writing or understanding the printed word.[3] Such a condition has been called "pure word deafness"; Wernicke, who thought that the phenomenon was correlated with a defect in conduction through subcortical layers of the temporal lobe from Heschl's gyrus to Area 42, stated that it was "exceedingly rare." Since his time few cases have been reported. It is the purpose of the present communication to report such a case, in which the defect in interpreting auditory stimuli extended beyond language to all sounds—complete auditory agnosia—and in which speech, reading, writing, and other cerebral functions were comparatively spared. Some of the interesting psychological manifestations in this case will be discussed. For comparison and contrast, a case of a more classic form of Wernicke's aphasia will be reported and discussed, with special reference to dysfunction of the temporal lobe.

REPORT OF CASES

CASE 1.—C. N., a single, right-handed man aged 45, an electrical and mechanical engineer, entered the Neurological Institute of the Presbyterian Hospital, New York, on Feb. 27, 1950, with the history that four days prior to admission he had suddenly experienced "numbness" in both hands, but more pronounced in the right. Upon trying to unlock his door, he had considerable difficulty with his key because he "could not feel" properly with his right hand. After entering the house and turning on the radio, he discovered that he could hear nothing. He could hear neither the sound of his own steps nor the sound of rapping on wood when he tested himself. He could, however, speak and read "if the sentences were simple." He imme-

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1. Wernicke, C.: The Symptom Complex of Aphasia, in Modern Clinical Medicine, edited by A. Church, New York, D. Appleton & Co., 1908, pp. 265-324.

2. Lichtheim, L.: On Aphasia, Brain **7**:433-484, 1885.

3. Stengel, E., and Hemphill, R. E.: A Study on Pure Word-Deafness, J. Neurol. & Psychiat. **3**:251-262, 1940.

diately called friends, who noted that he seemed "confused and dazed" and that his speech was garbled. During the next few days he stated that some hearing returned but that all sounds seemed "confused" to him and that music was a meaningless jumble of sound. His speech rapidly improved, and he was referred to the hospital about 10 days after the onset of his illness.

Medical History.—Four years prior to admission the patient had had an episode during which he found himself suddenly unable to read. It was not well remembered whether, in this first attack, he had had difficulty with both articulate speech and comprehension of the printed word. He recovered quickly and completely within two days. There was no other significant history of past illness.

Social History.—The patient was born in Germany, the third of four children. No serious childhood illnesses were recalled. He attended primary and secondary school and then a mechanical-engineering school in Germany, obtaining a scientific degree in that field at the age of 23. He studied English while in school but could not speak it fluently or without an accent. In 1927 the patient came to the United States and worked with various firms, from which he received letters of recommendation; he eventually participated in the formation of a steel-manufacturing concern, which failed in 1946. Since that time he had had financial difficulties upon repeated attempts to reorganize his business, but he continued work as a designing engineer.

No history of gross psychosocial disturbance in his family environment was elicited. He was a bachelor and had numerous friends, who considered him somewhat shy. He had had sporadic heterosexual relationships. He was fluent in English before his illness, used to read, and was fond of music, although he played no instrument. There was no history of alcoholism, drug intake, or overt mental illness.

Physical Examination.—The patient was a well-developed, alert man, weighing 160 lb. (72.6 kg.). The pulse rate was 78, and the blood pressure, 120/80. Physical examination of the heart, chest, and abdomen showed no abnormality. Neurological examination revealed no abnormalities of strength, coordination, reflexes, or sensation in any modality. (Instructions were communicated to the patient by writing and gesture, and he cooperated quickly and easily.) Cranial-nerve function was normal.

Laboratory Examination.—The hemoglobin content was 15 gm. per 100 cc., and the white blood cell count, 9,300, with a normal differential count. The urine was normal, and the Mazzini test gave a negative reaction. The spinal fluid was under an initial pressure of 180 mm. of water, with 1 lymphocyte per cubic millimeter, 42 mg. of protein per 100 cc., a negative Wassermann reaction, and a normal colloidal gold curve. X-ray studies of the skull and chest showed nothing abnormal. Repeated audiometric examinations finally overcame the patient's difficulty with comprehension and revealed a mild hearing loss, extending through all frequencies, with a maximum of 40 db. on the right and 25 db. on the left. It was repeatedly noted in the hospital that the patient's auditory acuity was good; in the ward he noted sounds of low intensity. Responses to caloric tests were normal. On one occasion the electroencephalogram showed a normal record; on another, slight generalized slowing. A pneumoencephalogram, obtained one year after the patient's admission, showed normal ventricles and slight increase in the amount of subarachnoid air.

Tests for Aphasia.—Spontaneous Speech: The patient generally spoke freely and quickly and usually in simple, but complete, sentences. He made frequent mistakes with tenses and occasionally used a word which was meaningless, but which resembled a word he wished to use. For example, when correcting a paragraph he had written, he said, "The whole damn thing must be build over." When describing a sound heard, he said, "It was something like a 'gribing.'"

Reading: He could read aloud slowly, occasionally reading a word erroneously, for example, "look" for "lock" and "mine" for "mind." He could paraphrase a paragraph read aloud or silently fairly well, forgetting several details. He followed fairly complicated commands read from cards (e. g., "Put your right hand on your left ear") but read slowly. He failed to comply correctly with the command, "Cross out every second 'e' in the sample sentence," and instead crossed out every "e." Upon correcting his own written productions, he often recog-

nized errors but would have great difficulty in deciding the correct word from two or three similar-sounding ones, for example, "mend" and "meant." It was, however, easily possible to converse with the patient by means of writing, although he would take several seconds to read the written question, one phrase or word at a time.

Naming: The patient named all varieties of objects correctly from sight and from their pictures. He was never at a loss for the correct noun.

Calculation: The patient was very quick on fairly long arithmetical problems from printed cards but stated he had lost the higher mathematical ability that he had been accustomed to use in his work; when tested with problems in long division, multiplication, and square root, he did them quickly and with ease, using pencil and paper. He was reading engineering books after a few months.

Writing: The patient wrote quickly with a clear, legible hand, the letters being formed separately, somewhat resembling printing. His sentences were rambling, long, often unpunctuated, and lacking in capitals; the present and past tenses were usually mixed to a chaotic degree. As has been mentioned, words that sounded alike were frequently misspelled. Examples of his account of his illness follow.

"I called up a friend of my for the first time I heard the bell and some talking but I could not understand the world."

"My right hand feeled like ice and I had no power to held even a keyes or cigarett in my hands."

Comprehension of Auditory Stimuli: It was in this sphere that the patient showed the most persistent and striking deficit. He behaved like a deaf person and only occasionally, even 18 months after the onset of his illness, could understand a few spoken words.

(*a*) Comprehension of sounds: The patient was seated beside a table on which were placed paper, ice in a glass of water, a bell, matches, a watch, and coins. He was instructed (by writing) that he would be blindfolded, a sound would be produced from one of the objects on the table, and he then would be unblindfolded and was to identify the object producing the sound.

A sample of his performance on this test follows:

Sound	Patient's Identification
Watch ticking	"Heard a sound, far, far away." Does not indicate watch or recognize it as source of sound when seen
Paper rattling	"Sounded like watch again"
Bell ringing	Points to bell
Ice rattling in glass of water	"Still same sound." Picks up bell
Water pouring from pitcher into glass	"Something like a 'gribing'"
Money jingling	Points to money. "Money"

This test was frequently repeated, with similar results, the patient usually naming less than half the objects correctly.

During interviews, various common street sounds came clearly through the open window. The patient clearly listened to these. He identified the sound of hammering correctly but identified the sounds of a car starting, car horns, and a siren as "someone talking" and "the wind in the leaves."

(*b*) Music: The patient had lost all ability to identify hummed or whistled melodies, which he had previously known well, for example, "Silent Night," "Blue Danube," or "Two Hearts in Three-Quarter Time." He stated he "could not understand" the music he heard on the radio. Nor could he sing or hum to himself as he used to do. He was tested repeatedly in the ensuing year and never regained recognition of simple tunes, even when the correct name was presented as one of a multiple choice. He could tell which of a series of three notes was the highest and the lowest but could not reproduce the tones. He had noted himself that he had difficulty in distinguishing notes less than an octave apart. When rhythms were tapped out, he could reproduce the part of the rhythm due to spacing of the taps, but not that part due to differences in intensity of tones; a corollary of this deficit was his loss of ability to dance because he could not perceive the rhythm.

(*c*) Words: The patient showed no comprehension of letters, words, or phrases (German or English) and could not distinguish sounds pertaining to language from gibberish. He learned to greet people and to tell them his condition when he met them, as he learned this was usually the first question asked.

(*d*) Repetition: Despite careful attention, the patient could not consistently repeat words, letters, or syllables spoken by the examiner. Examples, expressed in phonetic symbols, follow.

Examiner	Patient
a	ɑI
ɪi	dʒɪi
ɔo	ɔo
a, ɔo	a:ɾ , dʒɪi
a	Sounds like e:rdə

The patient could do much better when permitted to lipread. He scarcely ever correctly repeated a word of two syllables from the sound, often approximating one syllable; for example, "doctor" he gave as "dot."

Psychometric Examination.—Six months after his admission testing revealed excellent memory, both recent and remote, intact orientation, and superior knowledge and judgment. There was no deficit in performance tests or in abstraction. The one test on which the patient did poorly, despite careful explanation, was the "absurdity test," in which he was to point out the absurdities in certain statements.

Course.—For four days after the onset of the illness the patient stated that he was "completely deaf," and he then began to hear sounds "in a confused way." During the 18 months that the patient was followed, he regained scarcely any ability to understand spoken words, although he occasionally would catch a single word or phrase. He learned to lipread gradually.

Beginning four months after admission, the patient began to have formed auditory hallucinations of voices, sometimes in English, sometimes in German. Occasionally he heard phrases or sentences, such as "Carl, we're going this way," or "It will be all right." Usually, however, he heard disconnected single words, and sometimes when someone was speaking English, he would hear German words briefly. His hallucinations were never accusatory or in the voice of anyone he knew; the patient always recognized them as being his own productions. The hallucination would frequently seem to come from the right side. He never had tinnitus or "unformed hallucinations." During the latter months of his hospitalization the hallucinations disappeared almost entirely.

Throughout the course of the patient's illness he complained of intermittent paresthesias of the right hand. On one occasion he was found comatose and cyanotic with involuntary movements of the left hand. It was considered that he might have had a seizure prior to being seen.

There was considerable discussion concerning the "functional" element in his illness. He showed considerable emotional lability and what was considered bizarre and inappropriate behavior—laughing and making rather silly jokes during testing. At other times he showed depression over his lack of progress or hostility to the staff because nothing seemed to help him regain his hearing. Because of the question of an emotional disturbance, two amobarbital-sodium interviews were attempted. The patient became slightly sillier, but showed no gross change in behavior and regained no ability to understand speech. Electric shock therapy was begun; but after the third treatment the patient became confused, disoriented, and inattentive, and it was discontinued.

The patient displayed a strong drive to regain normal function and a position in society. He read engineering handbooks (with some difficulty, but from which he drew diagrams) and psychiatric books, looking for possible therapy. At the time of this report, he had regained his writing ability to the point where he made almost no errors; he still read slowly.

Comment.—It should first be said that this patient did not have completely isolated "pure word deafness," as defined. Weisenburg and McBride [4] pointed out that it is doubtful whether any case of truly isolated word deafness has ever been described. In this patient's writing there were occasional errors; his reading was slow and inaccurate at the onset of his illness. These difficulties, however, were slight as compared with his total loss of ability to interpret auditory stimuli; furthermore, during the period of observation, writing and speech improved almost to normal, reading remained slightly slow, but "word hearing" showed almost no improvement.

It has fairly generally been accepted that the pathological processes correlated with "auditory agnosia" are found in the first and second convolutions of the dominant temporal lobe, and occasionally bilaterally.[5] The course of this patient's illness suggests that at the onset he suffered a cerebrovascular accident affecting a large section of the parietotemporal area of the left cerebral hemisphere (as evidenced by numbness of the right hand and difficulty in reading, associated with difficulty in hearing), and that function returned to a large part of this area, with major deficit remaining in the function of the posterior temporal lobe.

It is apparently rare that the failure to identify and interpret acoustic stimuli becomes as generalized as in this patient. The profound loss of appreciation of rhythm and of simple tonal differences has, however, long been known as a manifestation of temporal-lobe damage.[5d] This patient's description of what he did hear is given almost in the same words as those used by patients in other reported cases, namely, "a wind in the trees, a murmuring, a foreign language." [6]

This patient's persistent statement that the onset of his disability was marked by total deafness is puzzling. True deafness in man on the basis of cerebral disease is extremely rare, but there are well-documented cases.[7] The pathological lesions have been bilateral—in auditory radiations, geniculate body, or temporal lobe. It is possible that this patient had bilateral temporal-lobe lesions and that the failure of his auditory perception to show any improvement is due to his having no normal minor area in the temporal lobe to retrain and "take over" function, as postulated by Nielsen.[8]

The formed auditory hallucinations in this patient also point to the temporal lobe as the site of the lesion. Such formed hallucinations are a recognized, though

4. Weisenburg, T., and McBride, K. E.: Aphasia: A Clinical and Psychological Study, New York, Commonwealth Fund, 1935.

5. (*a*) Stengel and Hemphill.[4] (*b*) Starr, M. A.: Organic and Functional Nervous Disease, New York, Lea Bros. & Co., 1907, p. 446. (*c*) Goldstein, K.: Language and Language Disturbances: Aphasic Symptom Complexes and Their Significance for Medicine and Theory of Language, New York, Grune & Stratton, Inc., 1948. (*d*) Henschen, S. E.: Klinische und anatomische Beiträge zur Pathologie des Gehirns, Stockholm, Nordiska Bokhandeln, 1920-1922, Vols. 5, 6, and 7; cited by Nielsen, J. M.: Agnosia, Apraxia, Aphasia, New York, Paul B. Hoeber, Inc., 1947.

6. Reinhold, M.: A Case of Auditory Agnosia, Brain **73**:203-223, 1950. Morel, F.: L'audition dans l'aphasie sensorielle, Encéphale **30**:533-553, 1935.

7. Thiébaut, E. L. J., and Wolinetz, E.: Verbal Deafness with Bilateral Hypoacusia Studied by Audiometer, Rev. neurol. **76**:93-94, 1944. Lemoyne, J.: La surdité corticale, Ann. oto-laryng. pp. 133-140, Oct.-Dec., 1944. Chavany, J. A.: Un cas de surdité d'origine corticale, Presse méd. **53**:472, 1945.

8. Nielsen, J. M.: Agnosia, Apraxia, Aphasia: Their Value in Cerebral Localization, Paul B. Hoeber, Inc., 1947.

uncommon, part of the symptomatology of temporal-lobe tumors and are rare with tumors elsewhere in the brain.[9] They occur also as aurae or components of seizures originating from foci in the temporal lobe, from which Penfield has reproduced them by electrical stimulation.[10] When, however, there are few other neurological signs and no known seizures (this patient may have had one), the hallucinations may be difficult to distinguish from the manifestations of a "functional" psychosis, as it was in this patient. One can speculate that this patient's hallucinations were correlated with abnormal electrical discharges from a focus of diseased tissue in the region of Area 42.

Further comment on the psychiatric status of this patient will be made in conjunction with that of the second patient to be reported on. This patient had complete Wernicke's aphasia, with paraphasia, alexia, and agraphia.

CASE 2.—B. I., a man aged 50, right-handed, a dentist, entered the Neurological Institute of the Presbyterian Hospital, New York, on May 1, 1950, with a history of having suddenly, one month prior to admission, awakened in the morning devoid of the ability to speak or to understand spoken or written words. He could not at that time repeat words spoken to him, and his speech seemed to be limited to the recital of a few perseverated sentences, such as "I wish I had the strength." There was no associated or prior phenomenon of muscular weakness, sensory disturbance, headache, nausea, or coma. In the months following the onset the patient had complained that his right arm had felt "numb." During the month prior to admission the patient had been agitated concerning his disability but had not recovered the ability to speak coherently. His family felt that they could communicate with him "on a simple level."

Medical History.—He had been in good health except for an episode nine years prior to admission, when he was hospitalized for two months for "heart pain." Records of this hospitalization were not available, but there was no history of signs or symptoms indicative of heart failure. The patient did on occasion indicate that since that time he had had periodic discomfort in the chest.

Social History.—The patient graduated from a dental school in New York and had practiced dentistry for over 20 years. He lived with an aged mother and two unmarried sisters, his wife having died 14 years previously. The patient was a Christian Scientist, was interested in church affairs, and had been very musical prior to his illness, having set lyrics to music. He had also written fiction in his leisure hours.

Physical Examination.—The patient was a frail, poorly developed man. The pulse rate was 100 and the blood pressure 150/95. Examination of the heart, chest, and abdomen revealed nothing abnormal. There were no abnormal findings on neurological examination except for the aphasia, described below, and very slight exaggeration of deep reflexes on the right over those on the left. There were no pathological reflexes.

Laboratory Data.—The hemoglobin content was 12.8 gm. per 100 cc.; the white blood cell count was 6,600, and the differential count was normal. The urine was normal, and the Mazzini reaction of the blood was negative. The spinal fluid was under an initial pressure of 165 mm. of water, with 1,100 red blood cells (slightly traumatic puncture) and 10 white cells per cubic millimeter. The protein measured 48 mg., and the sugar 68 mg., per 100 cc. Blood cultures were sterile, and the Wassermann reaction was negative. X-ray studies of the skull revealed nothing abnormal. An electrocardiogram revealed a left bundle-branch block, suggesting myocardial fibrosis, and a second (later) record showed no change.

Examination for Aphasia.—Spontaneous Speech and Behavior: The patient was agitated, restless, and in constant motion, making quick, repetitive gestures with his hands, such as

9. Tarachow, S.: Clinical Value of Hallucinations in Localizing Brain Tumors, Am. J. Psychiat. **97**:1434-1442, 1941. Paillas, J. E., and Tamalet, J.: Les tumeurs temporales: Considérations anatomo-cliniques à propos de 72 tumeurs verifiées, Presse méd. **31**:550-554, 1950.

10. Penfield, W., and Rasmussen, T.: The Cerebral Cortex of Man, A Clinical Study of Localization of Function, New York, The Macmillan Company, 1950.

fanning himself or fingering his clothes. He was attentive to the examiner and the tests; but when he had difficulty with a task, he tended to become even more agitated and abandon the effort. When asked a question, he spoke in reply almost continuously and had to be interrupted. His language consisted of disjointed, but well articulated, phrases and short sentences somewhat related to the question. When asked how he felt, for example, he would say, "Well, yes, that is, fairly well, oh, very hot in here . . . . yes, could be . . . . thank you so much." He never hesitated while appearing to search for a word and never seemed aware of impaired speech. Speech was copiously supplemented by exaggerated gestures to illustrate his meaning. He did not use incomprehensible words or jargon.

Repetition: Repetition of short single words was good, but that of even short phrases was markedly impaired, the patient usually repeating the first two words correctly, but never more.

Recognition of Written Words: From a list of words shown him, the patient could pick out the correct names for objects presented, and he could pronounce the words. Reading sentences aloud, however, confused him, and he soon stumbled to a halt. He could not do simple commands from printed cards.

Recognition of Spoken Words: He showed almost complete inability to point to an object when its name was spoken, nor could he select the proper name of a certain object from a series of spoken words. He could, however, always, select the correct printed word and pronounce it. He could not perform commands by spoken request.

Naming: The patient could name scarcely anything and always indicated by gesture or in broken phrases the use of the object.

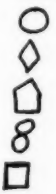
Writing: The patient wrote his name and address well, wrote a few words correctly from dictation ("penny," "key") but failed on most, producing, for example, "bo—bolee" for "button," and "pencob" for "pencil." He could not write spontaneously.

Calculation: This function was grossly impaired. He could do very simple problems but often confused the addition and multiplication symbols.

Abstraction Tests: Here, also, his performance was grossly defective. He could not reproduce simple angles or patterns made with match sticks (Goldstein stick test),[5c] nor could he copy the simplest patterns made with Goldstein-Scheerer blocks. When given parts of familiar figures to copy, he would, instead, draw the complete figure, for example:

Sample Given

Patient's Drawing



Course.—While in the hospital, the patient was continually hyperactive and agitated. One night after a thunderstorm he was found sitting on the edge of his bed, pale, confused and terror-stricken, saying incoherently, "Lightning, all of a sudden, bang, went through me," meanwhile illustrating his words by striking his forehead. On another occasion he became very agitated and made an unprovoked and purposeless assault on a male nurse who was carrying food trays into the ward.

The patient improved little while in the hospital and was seen again after having been at home one year. His sister stated that he had been able to carry on some dental practice, that she could make herself understood to him, and that he read the *New York Times* with interest and profit.

Examination at this time revealed the following status:

Spontaneous Speech: This was improved, consisting of hurried, somewhat disjointed, simple phrases and sentences, accompanied by no dysarthria but by much gesture.

Comprehension of Spoken Words: The patient could follow simple spoken commands well but became confused when more than one simple act was involved. His repetition was slightly better than on initial examination, but he still could remember only the first few words. He would attempt to cover up his failure by hurried, rambling speech on the subject suggested by the sample sentence.

Comprehension of Written Words: He read aloud almost perfectly. When asked to give the meaning of a short paragraph read silently, he merely spoke on the general topic suggested by a few key words of the paragraph but gave no coherent paraphrase. He made several mistakes in following written instructions concerning drawing lines in simple figures.

Various Tests: Naming was still grossly defective, but he selected the correct name from several spoken. Calculation was much improved, the patient being able to do problems in long division and multiplication with ease, although he occasionally mistook a + for an ×.

Writing: He copied perfectly, and when ask to write about his condition, he wrote, "I feel so much better now and hope to improve. I'm trying so hard to get better. I'm doing myself." From dictation he wrote correctly only the first few words.

Abstraction Tests: He performed the Goldstein stick test quickly and with ease; he was slow on a few block designs but accomplished most designs quickly. He accurately crossed out every "e" from a given sentence but missed several when asked to cross out every second "i."

Comment.—The onset of illness was abrupt in the second case, as in the first, and the deficit was maximal at the beginning, a characteristic of a vascular lesion. The severe sensory aphasia, combined with paraphasia and absence of other neurological signs, suggests that the lesion in the second case was also preponderantly in the dominant temporal lobe, but the more generalized deficit, including alexia, acalculia, and loss of abstract ability, suggests also that a fairly large temporoparietal area was involved.

The differences in symptoms in the two patients are clear, the second showing a complete syndrome of auditory agnosia, disordered but abundant speech (paraphasia), alexia, and partial agraphia. After a year's convalescence, the first patient's condition was almost intact except for the "word deafness," which remained unimproved. The second patient, however, though having a much more generalized deficit, never had the complete auditory agnosia of the first patient, and recovered much auditory function during the year.

The behavioral disorders displayed by these patients deserve comment. The difficulty in differentiating auditory agnosia and a psychiatric, or purely functional, disorder is great. This difficulty is shown by the history of the first patient and by that of Reinhold's [6] patient, who was in a mental hospital nine months before the correct diagnosis was made. Such patients act like the deaf, but it soon becomes obvious that they hear slight sounds, the immediate conclusion being that their disability is psychogenic. The same fate frequently befalls children who are afflicted with a congenital form of this disorder.[11] When the cerebral defect is greater, as in the second patient, the neurological condition is more obvious, but even this patient impressed the admitting intern, who saw him briefly in the emergency ward, as hysterical.

Although these cases of aphasia are frequently mistaken for cases of functional psychosis, the differentiation is not entirely an either-or matter.

11. Worster-Draught, C.: Congenital Auditory Imperception (Congenital Word Deafness) and Its Relation to Idioglossia and Allied Speech Defects, M. Press **210**:411-417, 1943.

The frequent association of actual psychosis and receptive aphasia has long been known and commented upon,[12] and patients who are not actually psychotic usually show profound mood and behavior disturbances. Nielsen [8] described these patients as euphoric and voluble and comparatively unable to cease talking. Both the patients in the present report showed abnormal behavior; the first was often silly and showed extreme emotional lability, and the presence of hallucinations has been commented upon. The second patient did not display euphoria but showed extreme anxiety and hyperactivity; at one time he was frankly psychotic in behavior, and probably hallucinated.

It has usually been assumed that these mental abnormalities in the aphasic patient are nonspecific psychological sequelae to the emotional trauma suffered by a person suddenly and severely deprived of his ability to communicate—a catastrophic reaction, to use Goldstein's phrase.[5c] There is some indication, however, that behavioral disturbance is a definite and specific manifestation of disease of the temporal lobes (as well as of the frontal lobes). Klüver and Bucy found striking behavioral change in monkeys after temporal lobectomy.[13] The original speculation by Papez that the hippocampal region of the temporal lobe was a key area in the regulation of emotional behavior has since been substantiated by a mass of data in experimental animals, notably that of Bard and Mountcastle, cited by MacLean.[14] Psychiatric disturbances of many kinds are common in temporal-lobe tumors.[15] Behavioral disorders are a common accompaniment of psychomotor epilepsy with temporal-lobe foci,[16] and peculiar states of consciousness have been produced in epileptic patients by stimulation of the temporal lobes.[10] It is suggested that the psychosis and severe behavioral and emotional disturbance in the cases reported here, and in other cases of sensory aphasia, may be a manifestation of specific dysfunction of the temporal lobes.

SUMMARY

1. A case of complete auditory agnosia ("pure word deafness") and one of Wernicke's aphasia are reported. The difference between the two syndromes is discussed.

2. Total deafness and auditory hallucinations occurred at different times in the course of the illness of the patient with auditory agnosia. Their significance is commented on.

3. Severe behavioral disturbance occurred in both patients. The difficulty of its differentiation from purely psychogenic disease is indicated, and its relation to temporal-lobe dysfunction is suggested.

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12. Kussmaul, A., and Wernicke, C., cited by Mills, C. K.: Aphasia ond Other Affections of Speech, in Some of Their Medico-Legal Relations, Studied Largely from the Standpoint of Localization, Rev. Insan. & Nerv. Dis. **2**:3, 1891-1892.

13. Klüver, H., and Bucy, P.: Preliminary Analysis of Functions of the Temporal Lobes in Monkeys, Arch. Neurol. & Psychiat. **42**:979-1000 (Dec.) 1939.

14. MacLean, P.: Psychosomatic Diseases and the "Visceral Brain": Recent Developments Bearing on the Papez Theory of Emotion, Psychosom. Med. **11**:338-353, 1949.

15. Alliez, J.; Paillas, J. E., and Tamalet, J.: Aspects psychiatriques des tumeurs temporales (à propos de 47 observations), Ann. méd.-psychol. **107**:67-70, 1949. Keschner, M.; Bender, M. B., and Strauss, I.: Mental Symptoms in Cases of Tumor of the Temporal Lobe, Arch. Neurol. & Psychiat. **35**:572 (March) 1936.

16. Gibbs, E. L.; Gibbs, F. A., and Fuster, B.: Psychomotor Epilepsy, Arch. Neurol. & Psychiat. **60**:331 (Oct.) 1948.

LIPIDS AND PROTEINS OF PLASMA IN PATIENTS WITH DISEASES OF THE NERVOUS SYSTEM

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THE BIOCHEMICAL defects in neurological and psychotic disorders are poorly understood. A recent review [1] indicates that investigators do not agree on the changes in the lipid constituents of blood plasma associated with epilepsy and the psychoses. Information concerning the effect of nervous diseases on plasma proteins is limited. The data presented in this paper are concerned with analyses of plasma lipids and proteins in patients with a variety of disorders of the nervous system.

METHODS AND MATERIAL

Twenty-six male medical students and staff members served as controls. The patients were divided into three groups: (*a*) neurological patients with and without complications; (*b*) psychotic patients with and without complications, and (*c*) subjects with a variety of medical and surgical disorders. The neurological diseases with complications included infections and inflammatory reactions (12 patients), neoplasms of the brain (2 patients), circulatory disturbances (11 patients), degenerative or demyelinating diseases (7 patients), metabolic or nutritional disturbances (4 patients), intoxications (2 patients), and trauma (1 patient). The neurological disorders without complications included infections and inflammatory reactions (18 patients), congenital defects (4 patients), neoplasms of the brain and spinal cord (8 patients), circulatory disturbances (1 patient), and degenerative or demyelinating diseases and conditions of unknown origin (22 patients). The psychoses with and without complications included schizophrenia (20 patients), manic-depressive psychosis (16 patients), involutional melancholia (5 patients), senile psychosis (3 patients), and post-traumatic psychosis (1 patient).

Blood was drawn into a heparin-moistened syringe before breakfast. The sample was immediately centrifuged and the plasma removed. Approximately 4 to 5 ml. of plasma was needed for electrophoretic and chemical analyses.

Plasma was diluted 1:3 with barbital buffer (pH 8.6; ionic strength, 0.1) and dialyzed in the cold room for 18 hours against three changes of this buffer. Electrophoretic analysis was carried out in the Tiselius apparatus at 2 C., the patterns being recorded by the scanning method of Longsworth.[2] Electrophoresis was done in a microcell of 2-ml. capacity for 90

This investigation was supported by Research Contract V1001M-1074, Veterans Administration.

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1. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry Interpretations, Ed. 2, Baltimore, Williams & Wilkins Company, 1946.

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minutes with a current of 8 ma. The areas of the components of the ascending patterns were measured.

The total lipids of the plasma and the ultracentrifuge fractions were extracted with hot acetone-absolute ethyl alcohol (1:1). Aliquots were analyzed for total and free cholesterol according to the procedures of Sperry and Brand.[3] The acetone-ethyl alcohol extract was evaporated to dryness, immediately extracted with petroleum benzin U. S. P., filtered, and brought to volume. Aliquots were analyzed for phospholipid [4] and sphingomyelin.[5]

RESULTS

The cholesterol and phospholipid concentrations of the plasma for the three groups of subjects are graphed in Chart 1. No group differences are noted for these

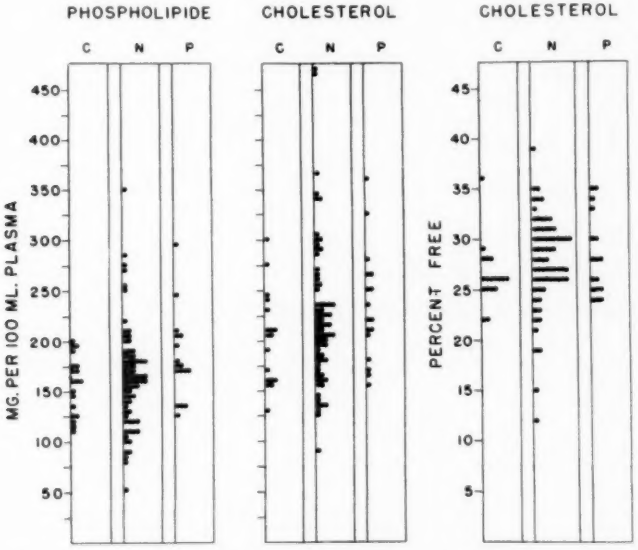

Chart 1.—Scatter diagrams of phospholipid and total cholesterol concentrations and the percentage of free cholesterol in the plasma. In this and in subsequent figures, the letters *C*, *N*, and *P* refer to controls and to neurological and psychotic patients.

lipid constituents by chi-square analysis. The elevated values for cholesterol and phospholipid in the plasmas observed in a number of cases do not appear to be typical for any specific disorder. The mean values for the percentage of free cholesterol in the three groups show no significant difference.

Sphingomyelin values of the plasma for the control, neurological, and psychotic patients are graphed in Chart 2. Statistical analysis of the data for the neurological

3. Sperry, W. M., and Brand, F. C.: Colorimetric Determination of Cholesterol, J. Biol. Chem. **150**:315-324, 1943.

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5. Schmidt, G.; Bennotti, J.; Hershman, B., and Thannhauser, S. J.: A Micromethod for Quantitative Partition of Phospholipide Mixtures into Monoaminophosphatides and Sphingomyelin, J. Biol. Chem. **166**:505-511, 1946.

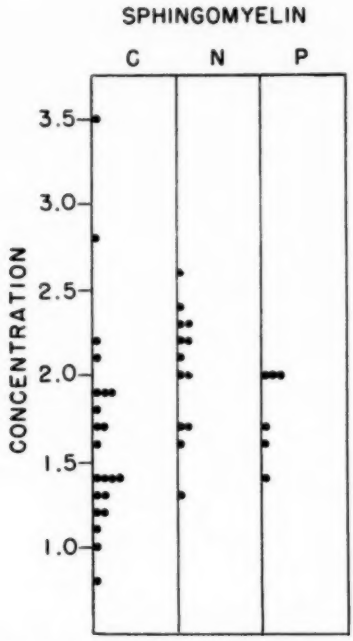

Chart 2.—Scatter diagrams of plasma-sphingomyelin concentrations.

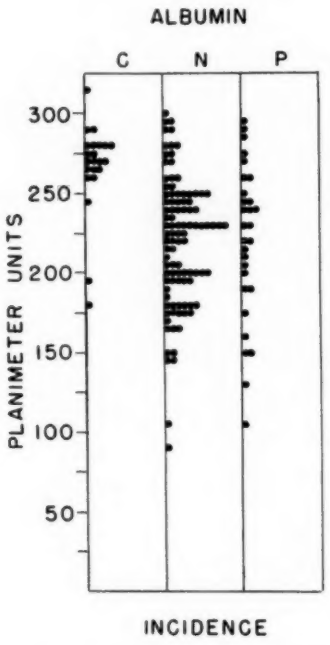

Chart 3.—Scatter diagrams of plasma-albumin concentrations determined by electrophoresis.

patients yields a chi-square value which shows a significant difference from that for the control group. The data available are insufficient to allow statistical evaluation for the psychotic group.

Electrophoretic patterns of plasma were analyzed for their albumin (Chart 3) and γ-globulin areas. During the course of these studies, it was found that minimal amounts of heparin, sufficient to prevent coagulation, had no influence on the electrophoretic pattern but that slight excesses of heparin influenced the distribution of the α-and β-globulins. Since it was difficult to control the amounts of heparin used in collecting blood samples, the data for the α-and β-globulins were omitted. The γ-globulin concentrations remain fairly constant in all cases studied. The total nitrogen of the plasmas of the three groups of patients shows no significant difference from the controls as analyzed by the chi-square method.

Analyses of plasmas of patients with medical or surgical disorders yielded results which were essentially the same as those reported for the neurological and psychotic groups.

A correlation of albumin concentration and age (19 to 70 years) in the psychotic patients who were free of organic disease yielded a coefficient of 0.04, indicating that the decreased albumin concentration is not influenced by the age of the patient.

COMMENT

Thannhauser [6] found that the sphingomyelin concentration of plasma remained fairly constant in a wide variety of diseases. In the present study, the plasma-sphingomyelin concentration is the only lipid constituent which is significantly increased in neurological disease.

The decreases in plasma-albumin concentration in both the neurologic and the psychotic group are similar to those observed in patients with acute or chronic diseases. The decreases noted would not appear to be due to the nutritional state, since Keys and associates [7] have shown that subjects on a semistarvation diet maintain a normal albumin concentration. The impairment in the production of plasma albumin, particularly in patients with psychoses uncomplicated by other disorders, undoubtedly reflects a metabolic or an endocrine disorder.

SUMMARY

The lipids and proteins of the plasma of patients with neurological and psychotic disorders have been determined. The phospholipid and cholesterol concentrations were not affected in these patients. There was evidence to suggest that the sphingomyelin concentration is elevated in patients with neurological diseases. The decrease noted in plasma-albumin concentration may represent a metabolic or an endocrine disturbance.

Mr. Edward R. Berry, Mr. T. J. Boyd, and Mr. Titus Pankey gave technical assistance.

6. Thannhauser, S. J.: Medical Progress: Serum Lipids and Their Value in Diagnosis, New England J. Med. **237**:515-522, 546-552, 1947.

7. Keys, A.; Brozek, J.; Henschel, A.; Mickelsen, O., and Taylor, H. L.: The Biology of Human Starvation, Minneapolis, University of Minnesota Press, 1950.

EXPERIMENTAL CHRONIC EPILEPSY IN THE MONKEY

Effect of Ablation of Contralateral Precentral Motor Cortex

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PREVIOUSLY it was reported [1] that section of the corpus callosum either before or after the application of alumina cream (suspension of aluminum hydroxide in water) to the precentral motor cortex of monkeys restricted subsequent epileptic seizures to the contralateral side. The attacks in animals with section before treatment with alumina cream were severer and more easily elicited than those usually observed in epileptic monkeys without section of the corpus callosum. Section performed in a group in which recurrent seizures had previously been established was rapidly followed by contralateral status epilepticus. These observations suggested not only that the corpus callosum played a major role in the spread of convulsive discharges from one cerebral hemisphere to the other, but that also its section might have intensified the resulting contralateral attacks through severance of "inhibitory" fibers from the opposite hemisphere.

It has been shown that subtotal ablation of the precentral motor cortex prior to the application of alumina cream to the same area did not inhibit the development of epileptic seizures. Furthermore, in monkeys in which seizures had been established before removal of the "focal cortical zone" a recurrence of characteristic attacks followed a long symptom-free interval.[2]

The present study is concerned with (*a*) the effect of subtotal ablation of a contralateral precentral motor cortex with the simultaneous application of alumina cream to the intact precentral motor cortex and (*b*) the application of alumina cream to the intact precentral motor cortex after subtotal ablation and alumina-cream treatment of the contralateral precentral motor cortex.

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1. Kopeloff, N.; Kennard, M. A.; Pacella, B. L.; Kopeloff, L. M., and Chusid, J. G.: Section of Corpus Callosum in Experimental Epilepsy in the Monkey, Arch. Neurol. & Psychiat. **63**:719-727 (May) 1950.

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TECHNIQUE

Disks containing test material were applied to Macaca mulatta, weighing approximately 7 lb. (3.2 kg.), as previously described.[3] Ablation of cortical tissue was performed by subpial suction through a craniotomy opening, with the animal under general anesthesia (pentobarbital sodium). Electroencephalograms were taken at appropriate intervals without the use of an anesthetic. The standard method of eliciting induced seizures was by vigorous prodding with a stick.[3] The seizures designated as "spontaneous" were those which were noted upon entrance

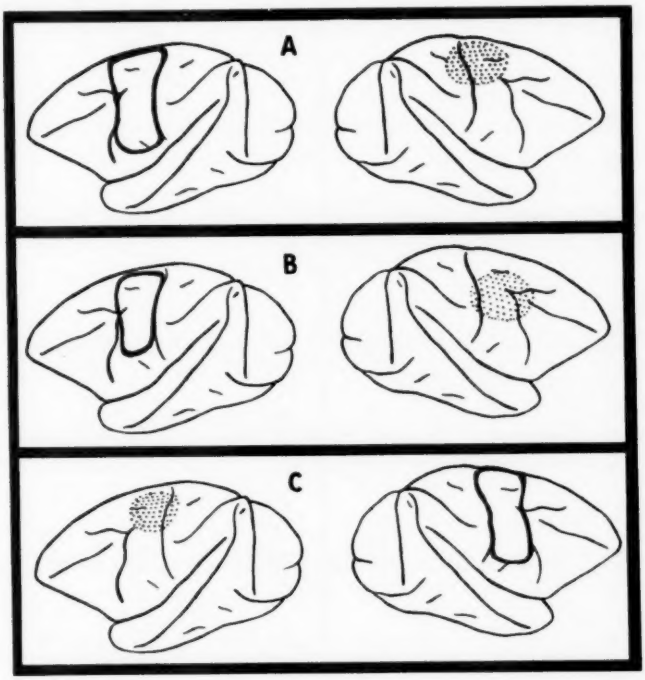

Fig. 1.—Ablation of contralateral precentral motor cortex with simultaneous application of an alumina-cream disk. The site of ablation is indicated by a heavy solid outline, and the position of the alumina-cream disk, by a dotted area. *A*, Monkey 585; *B*, Monkey 586; *C*, Monkey 591.

of the observer into the room or upon approaching the cage. At the termination of the experiment, a map of each brain was made indicating the site of application of the disk and the extent of ablation (Figs. 1 to 3).

3. Kopeloff, N.; Kopeloff, L. M., and Pacella, B. L.: The Experimental Production of Epilepsy in Animals, in Hoch, P. H., and Knight, R. P., Editors: Epilepsy: Psychiatric Aspects of Convulsive Disorders, New York, Grune & Stratton, Inc., 1947, p. 163.

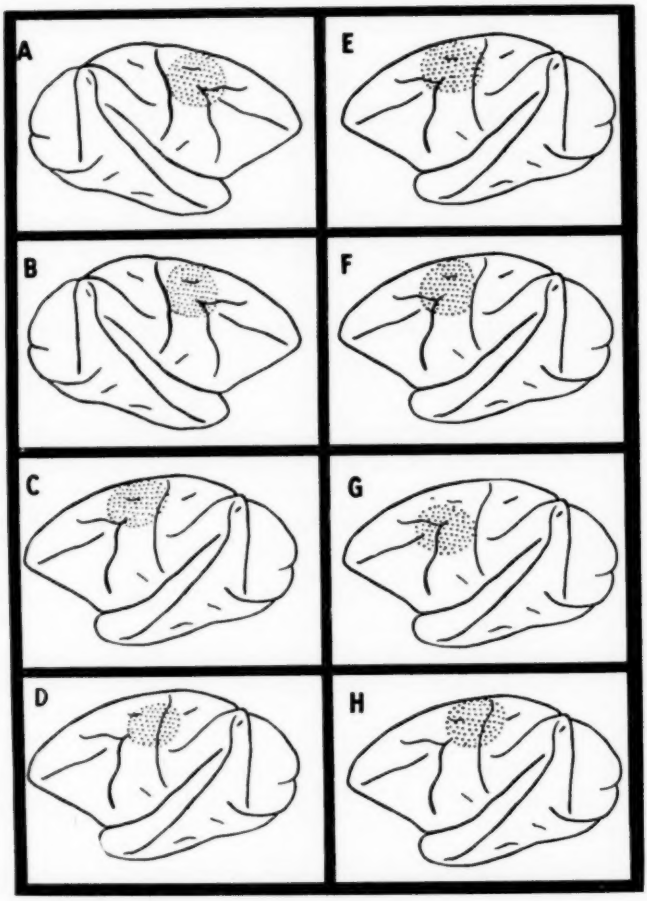

Fig. 2.—Area of application of alumina-cream disk (dotted) to one precentral motor cortex in eight controls: *A*, Monkey 584; *B*, Monkey 587; *C*, Monkey 530; *D*, Monkey 532; *E*, Monkey 578; *F*, Monkey 583; *G*, Monkey 485; *H*, Monkey 498.

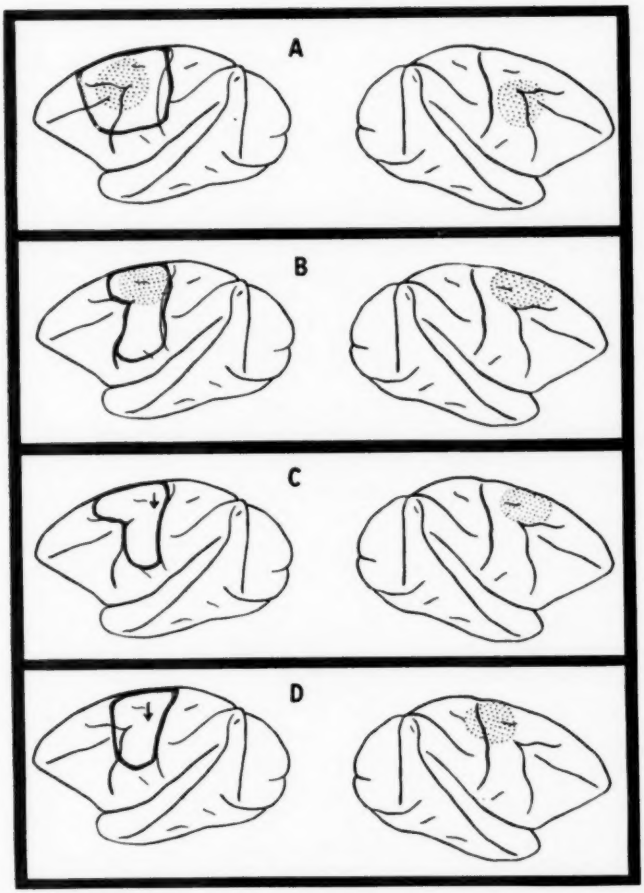

Fig. 3.—Application of alumina-cream disk to right (control) precentral motor cortex after ablation of contralateral (left) precentral motor cortex (heavy solid outline) and alumina-cream treatment of the ablated site (dotted area). Arrows in *C* and *D* indicate site of injection of alumina cream. *A*, Monkey 464; *B*, Monkey 515; *C*, Monkey 512; *D*, Monkey 513.

TABLE 1.—*Ablation of Precentral Motor Cortex Performed Simultaneously with Application of Alumina Cream to Contralateral Precentral Motor Cortex*

Monkey No.	Fig.	Ablation Date	Ablation Side	Alumina Lot No.	Alumina Date	Alumina Side	Maximal EEG Abnormality L	Maximal EEG Abnormality R	Onset After Alumina, Mo.	Induced Seizures No. of Mo. Observed*	Induced Seizures No. of Seizures	Induced Seizures No. of Times Stimulated	Spontaneous Seizures Months After Application of Alumina 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Total
585	1*A*	11/22/49	L	150	11/22/49	R	+	++±	1½	16	8	11	..	1	1	..	..	..	..	2	..	1	1	1	2	..	1	1	11
586	1*B*	12/13/49	L	150	12/13/49	R	+++	++	1½	16	10	10	..	2	1	1	..	1	1	..	1	..	..	1	2	..	..	..	10
591	1*C*	3/ 7/50	R	150	3/ 7/50	L	+++±	+++	1¼	6	4	4	..	6	2	1	..	1	..	..	..	..	..	..	..	..	..	..	..	10
Controls		Dural Flap																											
584	2*A*	12/ 1/49	L	150	12/ 1/49	R	+++	++±	2	13	11	13	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0
587	2*B*	12/20/49	L	150	12/20/49	R	++	+++	1½	14	9	16	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0
530	2*C*	.....	..	150	7/ 8/47	L	+++±	+++±	2	14	15	15	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0
531	...	.....	..	150	7/ 8/47	L	++±	++±	4½	17	11	15	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0
532	2*D*	.....	..	150	11/13/47	L	+++	+++	1⅓	12	6	10	..	1	..	..	..	..	..	..	..	..	1	..	..	..	..	1†	2
578	2*E*	.....	..	150	5/10/49	L	+++±	+++±	4	12	16	17	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1
583	2*F*	.....	..	150	6/29/49	L	+++±	+++	2½	5	5	5	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0

* From time of first seizure.
† 21st month.

TABLE 2.—*Application of Alumina Cream to Precentral Motor Cortex After Alumina Cream Treatment of Ablated Contralateral Precentral Motor Cortex*

Monkey No.	Fig.	Ablation Date	Ablation Side	Alumina on Ablated Site: Mo. After Ablation	Alumina on Ablated Site: Date	Alumina on Ablated Site: Duration of Seizures, Mo.	Maximal EEG Abnormality L	Maximal EEG Abnormality R	Interval After First Alumina Treatment, Mo.	Alumina on Intact Cortex: Lot No.	Alumina on Intact Cortex: Date	Alumina on Intact Cortex: Side	Maximal EEG Abnormality L	Maximal EEG Abnormality R	Onset After Alumina, Mo.	Induced Seizures: No. of Mo. Observed	Induced Seizures: No. of Seizures	Induced Seizures: No. of Times Stimulated	Spontaneous Seizures Months After Application of Alumina 1	2	3	4	5	6	7	8	9	10	11	17	20	21	Total
464	3*A*	2/20/45	L*	14½	5/ 8/46	0	+	+	9	141	2/19/47	R	++	++++	1½	19	10	14	..	2†	..	..	1	..	..	1	1	..	..	1	..	7
515	3*B*	3/14/47	L	3½	6/24/47	0	0	0	16	150	10/26/48	R	.....	.....	1	..	..	..	..	‡	..	..	..	..	..	..	..	..	..	..	..	..	..
512§	3*C*	2/ 7/47	L	3	5/ 9/47	0	+	+	17½	150	10/26/48	R	.....	.....	1	..	..	..	..	‡	..	..	..	..	..	..	..	..	..	..	..	..	..
513§	3*D*	1/30/47	L	3½	5/12/47	5½‖	+++	++	18	150	11/ 9/48	R	.....	.....	½	..	..	..	‡	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Controls																			..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
485	2*G*	.....	..	....	.....	..	..	..	..	141	11/13/45	L	+++	++	1½	5	28	28	..	1	2	..	..	..	..	..	..	..	..	..	..	..	..
498	2*H*	.....	..	....	.....	..	..	..	..	141	6/ 4/46	L	++±	++	3½	30	18	32	..	..	..	..	1	..	..	..	..	..	..	..	..	..	3
522	...	.....	..	....	.....	..	..	..	..	141	3/25/47	L	.....	.....	1	19	1	18	..	2	..	..	..	..	..	..	..	..	..	..	..	..	1
530	2*C*	.....	..	....	.....	..	..	..	..	150¶	7/ 8/47	L	+++±	+++±	2	14	15	15	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2
531	...	.....	..	....	.....	..	..	..	..	150	7/ 8/47	L	++±	++±	4½	17	11	15	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0
532	2*D*	.....	..	....	.....	..	..	..	..	150	11/13/47	L	+++	+++	1⅓	12	6	10	..	1	..	..	..	..	..	..	..	..	..	1	..	..	1
578	2*E*	.....	..	....	.....	..	..	..	..	150	5/10/49	L	+++±	+++±	4	12	16	17	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2
583	2*F*	.....	..	....	.....	..	..	..	..	150	6/29/49	L	+++±	+++	2½	5	5	5	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1
																			..	..	..	..	..	..	..	..	..	..	..	..	..	..	0
																			..	..	..	..	..	..	..	..	..	..	..	..	..	..	0

* Ablation performed by electrocautery in infancy.
† Bilateral status epilepticus initially.
‡ Bilateral status epilepticus; animal died after one week.
§ Alumina injected beneath ablated site.
‖ No seizures after March 22, 1948.
¶ Values for Lot 150 controls are repeated from Table 1

RESULTS

In three monkeys (Table 1) alumina cream was applied to one precentral motor cortex immediately after subtotal ablation of the contralateral precentral motor cortex. As controls, two monkeys were similarly treated with alumina cream immediately after a dural flap had been made in the contralateral precentral motor area. Five monkeys which had been treated previously with the same alumina-cream preparation (Lot 150) on one precentral motor cortex were used as controls of epileptogenic activity. It may be seen from Table 1 that all three of the test animals (monkeys 585, 586, and 591) exhibited a significant number of "spontaneous" seizures. In comparison, the control animals with dural flaps (monkeys 584 and 587) exhibited no "spontaneous" seizures, while of the five additional control animals two showed minimal "spontaneous" seizure activity. From the data presented no appreciable difference in time of onset of seizures or of induced seizure reactivity was evident. Evaluation of electroencephalograms on the basis of the maximal degree of abnormality produced did not disclose a significant difference between the test and the control groups.

In four monkeys (Table 2) subtotal ablation of one precentral motor cortex was followed 3 to 14 months later by treatment of the ablated site with alumina cream, applied either in a disk or by local injection. The results with three of these monkeys (515, 512, and 513) have been described elsewhere.[2] It was shown that ablation of various portions of the precentral motor cortex did not prevent the development of seizures upon subsequent application of alumina to the ablated or adjacent area, except in monkeys 515 and 512. Monkey 513 had onset of seizures five months after injection of alumina. These continued to occur for 5½ months and were followed by a period of nonreactivity, lasting 7½ months. In monkey 464, not included in the previous series, in which ablation had been performed in infancy, no seizures occurred after the application of alumina to the ablated site 14½ months later.

Nine to 18 months after the application of alumina to the ablated site, a disk of alumina cream was placed over the contralateral (right) precentral motor cortex. In each case status epilepticus (bilateral, predominantly left-sided) occurred ⅓ to 1½ months later. Despite the daily administration of phenobarbital sodium, 1 grain (0.065 gm.), subcutaneously, three of the four monkeys (515, 512, and 513) died in status epilepticus one week later.

In the control series (Table 2) both lots of alumina cream (141 and 150) induced the usual type of chronic recurrent convulsive activity and electroencephalographic changes without the appearance of status epilepticus. However, Lot 141 was more active than Lot 150, as evidenced by a greater incidence of "spontaneous" seizures.

COMMENT

It would appear from the data presented that the simultaneous or prior ablation of the contralateral precentral motor cortex of Macaca mulatta predisposes to an increased epileptic response to alumina cream applied to the precentral motor cortex. The possibility of interruption of "inhibitory" fibers or mechanisms by the ablation should be considered. The observation of Blum,

Blum, and Chow [4] that cortical ablations rostral to the superior postcentral sulcus render monkeys particularly vulnerable to amphetamine (benzedrine®)-induced seizures lends support to this view. Such a hypothesis is consistent with the increased convulsive reactivity produced by section of the corpus callosum in epileptic monkeys previously mentioned.[1] "Inhibitory" fibers may project from the contralateral precentral motor cortex through the corpus callosum, so that they may be functionally interrupted at either the callosal or the cortical level.

In no instance did ablation of the contralateral precentral motor cortex inhibit or decrease the convulsant effect of alumina cream applied to the precentral motor cortex. From this it may be inferred that an intact contralateral precentral motor cortex is not essential for the production of convulsive seizures.

Local vascular, tissue, and other changes associated with ablation should be considered as factors. Destruction or ablation of contralateral precentral motor cortical tissue by means of other physical, chemical, or related techniques, which could have served in further controlling the evaluation of the changes associated with our ablation procedure, were not employed. The control animals therefore served principally to demonstrate the activity of the alumina preparations used.

In Table 1, the chief evidence of an increased convulsant response was the appearance of a significantly greater number of "spontaneous" seizures with the same alumina-cream preparation (Lot 150), the epileptogenic effectiveness of which remained unchanged over a period of two years when stored at 4 to 5 C. Since alumina-cream preparations vary in their epileptogenic capacity, it is necessary to establish the degree of activity by suitable controls.

Table 2 presents the effect of alumina cream applied to the untreated cortex of animals previously studied.[2] These monkeys were included in a series in which it was demonstrated that the application of alumina over an ablated precentral motor area still caused characteristic clinical and electroencephalographic manifestations of epilepsy. Three of the four animals for which results are recorded here are the exceptional animals which failed to exhibit seizures. It is to be noted that in every instance bilateral status epilepticus occurred within 1½ months after the second application of alumina cream. These findings also suggest the possibility that the contralateral ablation removed an inhibiting or a suppressing effect of the precentral motor cortex. However, alumina-cream treatment per se on the ablated site may have facilitated the production of seizures, and this raises the further question of the capacity of a second application of alumina cream at another site to accentuate an active focus or to reactivate a quiescent focus.

SUMMARY

Application of alumina cream (suspension of aluminum hydroxide in water) to the intact precentral motor cortex with simultaneous subtotal ablation of the contralateral precentral motor cortex in three monkeys induced a greater degree of convulsive reactivity than in a control series of seven monkeys without ablation similarly treated with alumina cream.

4. Blum, R. A.; Blum, J. S., and Chow, K. L.: Production of Convulsions by Administration of Benzedrine® Following Brain Operations in Monkeys, Arch. Neurol. & Psychiat. **64**:685-691 (Nov.) 1950.

The application of alumina cream to the intact precentral motor cortex in four monkeys which had been treated 9 to 18 months previously with alumina cream at the site of ablation of the contralateral precentral motor area resulted in status epilepticus. Three of the animals died within one week after the onset of status epilepticus.

The existence in the precentral motor cortex of the monkey of "inhibitory" fibers or mechanisms whose interruption at the cortical or callosal level facilitates convulsive reactivity is suggested.

Dr. Margaret A. Kennard performed some of the earlier ablations, and Miss Frances Simpson gave technical assistance.

STATISTICAL CONTROL STUDIES IN NEUROLOGY

II. The Pronator Sign of Wilson

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AND
JACQUES M. MADONICK, M.D.
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THIS ARTICLE is the second of a series of papers dealing with the incidence of neurologic signs in "control groups." The first paper presented the results of the study on the Babinski sign.[1] Further investigations have emphasized the value of such control studies from several points of view. In addition to the light thrown on the clinical value of the particular sign, these studies have revealed the frequency of abortive and subclinical forms of various diseases of the nervous system.

Pronation of the outstretched hand and forearm was described by Wilson [2] as a "little sign" in acute chorea. A pronator sign was described by Strümpell [3] in 1901 as an early sign of pyramidal-tract disease. It was studied again by Babinski [4] in 1907 and by Gierlich [5] in 1925. These three investigators pointed out that pronation of the forearm and hand at rest and when outstretched is an early sign of pyramidal-tract disease. The clinical phenomenon reported in this study is apparently not related to pyramidal-tract involvement and is elicited in a different manner by quickly bringing the upper limbs in extension above the head. It is unfortunate that these two signs are known in the literature by the same name. It may be advisable to designate the sign discussed in this paper as the Wilson pronator sign.

MATERIAL AND METHOD

In order to determine the incidence of this sign in the general population, we examined 2,500 unselected, non-neurologic patients in a city hospital. In addition, we investigated its incidence in patients with various extrapyramidal syndromes, as listed in the accompanying table. In testing for the sign, we requested the patient to extend the upper limbs before him and then to elevate them above the head. The rapidity of the extension of the upper limb above the head was not a factor. A positive sign was one in which there was hyperpronation of the hands, on one

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or both sides, immediately or a few seconds after extension of the upper limb above the head. Occasionally hyperpronation was evident soon after the upper limb was extended directly forward. All the patients were examined thoroughly from the neurologic standpoint. We found no positive correlation of the pronator sign with the presence of pyramidal-tract signs. The Babinski sign was elicited in 12 (2.1%) of the 563 patients with a Wilson pronator sign. The incidence of the Babinski sign in the control series of 2,500 non-neurologic patients was 4.3%. In none of the 12 patients with both a Babinski and a pronator sign were there signs of pyramidal-tract involvement, such as tendon hyperreflexia, weakness, or spasticity.

RESULTS AND COMMENT

The table indicates that the sign was positive in 22% of the 2,500 patients in the hospital group. When we exclude the 252 patients with rheumatic fever and active or inactive rheumatic heart disease, in 72.6% of whom the sign was positive, the incidence becomes 16% for the remaining 2,248. The Wilson pronator sign was unilateral in 21% of the patients in the rheumatic group and in 26% of the patients who had the sign but no rheumatic involvement. The incidences of involvement of the right and left sides seemed about equal in the unilateral cases. In the series of 2,500, the sign was positive in 42% of patients under 19 and in 17% of those over 19 years of age. Age itself is apparently not a factor, since 29% of all the patients in the hospital series under 19 years of age had rheumatic fever, with or without cardiac involvement, and only 8% over 19 had rheumatic disease. The relatively high incidence of the Wilson pronator sign in children may be explained partly by the frequency of rheumatic fever in that group and the greater tendency to rheumatic encephalopathy (Costero [6]). There was no evidence of pyramidal disease in the children with a positive pronator sign. None of the patients below the age of 19 had both Babinski and a Wilson pronator sign. Lack of cooperation may have played a role in a few instances. Sex had no importance in accounting for the presence of the sign. A positive sign was found in 20% of the males and in 23% of the females.

Incidence of the Wilson Pronator Sign in Non-Neurologic Patients and in Patients with Various Extrapyramidal Syndromes

Diagnosis	No. of Patients	Patients with Positive Pronator Sign	
		No.	%
Non-neurologic disorders (hospital series)	2,500	563	22.5
Rheumatic fever; active and inactive rheumatic heart disease	252	183	72.6
Hospital series with omission of Group 2	2,248	380	16.9
Acute chorea	103	94	91.0
Degenerative chorea	16	12	75.0
Dystonia musculorum deformans	13	10	77.0
Parkinsonism	350	1	0.003

Numerous studies have shown cerebral alterations in cases of rheumatic fever with and without cardiac disease even in the absence of chorea (von Santha [7];

6. Costero, I.: Significado de la linfocitosis intersticial en el reumatismo y en otros procesos inflamatorios con una interpretación global de la principales lesiones reumaticas, Arch. Inst. cardiol. México **16**:471, 1946.

7. von Santha, K.: Über Gefässveränderungen im Zentralnervensystem bei Chorea rheumatica, Arch. path. Anat. **287**:405, 1932.

Breutsch,[8] Kernohan, Woltman, and Barnes[9]; Bodechtel[10]; Awzen[11]; de Gortari, Pellón and Costero[12]; Sacks[13]; van der Horst[14]; High and Aegerter[15]; Benda[16]). There is no mention of the Wilson pronator sign in any of these studies. This sign is sometimes evidence of cerebral involvement.

As noted previously, Wilson[17] considered the pronator sign a minor one in chorea. However, he gave no figures as to its frequency in this disease. He considered it indicative of the partial release from voluntary control of mechanisms completely released in decerebrate rigidity. Shaskan[18] also mentioned its presence in chorea but cited no figures. Hoff and Schilder[19] were of the opinion that the sign was due to cerebellar involvement.

Some of the patients with a Wilson pronator sign and without gross clinical evidence of rheumatic involvement of the heart had roentgenographic and fluoroscopic examinations of the chest and electrocardiographic studies. Thirty-six patients, all over 20 years of age, with positive signs were x-rayed. Two had mitral configurations, and two showed enlargement of the left ventricle. Of these 36 patients, 6 had abnormal electrocardiograms; 3 had a P-R interval greater than 0.21 sec.; 1 had a QRS complex of more than 0.11 sec.; 1 showed a diphasic and notched P-wave in lead II, and 1, an inverted and diphasic T-wave in lead I. These abnormalities were much more frequent than in electrocardiograms of so-called normal persons, as shown in the available control studies of Lewis and Gilder[20]; Shipley and

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Halloran [21]; Hoskin and Jonescu [22]; Fox, Klements, and Mandel [23]; Ashman [24]; Johnson [25]; Stewart and Manning [26]; McGinn and White [27]; Larsen and Skulason,[28] and Hall, Stewart, and Manning.[29] A control series of 36 patients without the Wilson pronator sign was studied in the same way. Abnormality in the electrocardiogram was found in only one instance, the result of a recent coronary-artery infarct. Three of the 36 patients with a pronator sign had organic cardiac murmurs. Of the group of patients who had a pronator sign without clinical evidence of rheumatic disease, careful anamneses revealed a history of chorea in 9, rheumatic fever in 18, frequent joint pain in 11, and frequent sore throat in 13.

The high incidence of this sign in cases of rheumatic fever or rheumatic heart disease, without chorea, points to the probability of cerebral involvement in a relatively high percentage of patients without other clinical evidence of chorea. This observation is corroborated by the report of de Gortari, Pellón, and Costero.[12] They found pathologic changes in the brain with no clinical neurologic signs or symptoms in 19.6% of their series of 107 patients with rheumatic encephalopathy.

SUMMARY AND CONCLUSIONS

The Wilson pronator sign was studied in a series of 2,500 non-neurologic patients admitted to a general hospital.

The sign was positive in 91% of patients with acute chorea, in 72.6% of 252 patients with all types of rheumatic fever with active and inactive rheumatic heart disease, and in 16.9% of the remaining 2,248 patients in the hospital series. It was present in 12 of 16 patients with chronic degenerative chorea, in 10 of 13 patients with dystonia musculorum deformans, and in only 1 of 250 patients with Parkinsonism.

Age and sex do not appear to be factors.

There is no evident relation to pyramidal-tract involvement. The high incidence in rheumatic fever and rheumatic heart disease is probably due to organic involvement of the brain.

1882 Grand Concourse (57).

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ELECTROMYOGRAM FROM ORBICULARIS OCULI IN NORMAL PERSONS AND IN PATIENTS WITH MYASTHENIA GRAVIS

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ELECTROMYOGRAPHY usually consists in recording action potentials from resting or voluntarily contracted muscles. In 1941 Harvey and Masland [1] introduced another procedure, in which potentials are recorded when the muscle is made to contract by supramaximal stimulation of the motor nerve. This method has the advantage of eliminating the vagaries of voluntary effort and so permits an objective analysis of the function of the peripheral nerve, neuromuscular junction, and muscle. One limitation of the procedure is that only muscles supplied by nerves accessible to electrical stimulation can be studied, so that to date only the muscles of the extremities have been tested.

An early sign of myasthenia gravis is weakness of the extraocular and facial muscles, which is not necessarily accompanied by any subjective or objective evidence of weakness of the extremities. In a series of 21 patients with myasthenia gravis studied by us,[2] all had facial weakness and ptosis or diplopia, but five had no clinical evidence of weakness of the extremities; for three of these five patients electromyograms recorded from the hand muscles were normal. It appeared desirable, therefore, to develop an electromyographic technique which could be applied to the facial muscles.

METHODS AND APPARATUS

The apparatus for amplification, recording, and stimulation was similar to that used by Harvey and Masland,[1] and Hodes, Larrabee, and German [3]; it has been described in detail elsewhere.[2] The facial nerve was selected for electrical stimulation. A 6-by-10-cm. copper (ground) electrode covered with gauze saturated with saline solution was placed at the nape. A circular silver-cup electrode, 7 mm. in diameter (cathode), was cemented to the skin anterior to the external auditory meatus at that point on the course of the facial nerve where threshold stimulation produced contraction of the orbicularis oculi muscle most readily. A similar electrode

This study was aided by a research grant from Hoffmann-LaRoche, Inc., Nutley, N. J.

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(anode) was attached to the skin about 2 cm. inferior to the cathode. Supramaximal electrical stimuli were used throughout the study. The duration of each stimulus was 0.5 msec. or less.

Action potentials were recorded from the orbicularis oculi muscle by placing a silver-cup (active) electrode 7 mm. in diameter, on the supraorbital region, another (indifferent) electrode on the infraorbital region, and a third (ground) electrode between the eye and the stimulating cathode.

All cup electrodes, filled with "redux" electrode paste, were attached to the skin by gauze squares saturated with collodion. Careful positioning of all electrodes was necessary to reduce the size of the stimulus artifact.

The recording camera was operated at a speed of 0.3 to 1.0 meter per second when normal subjects were studied, and at 0.1 to 0.2 meter per second in all other instances.

PROCEDURE

The subject was seated comfortably. Stimulating and recording electrodes were fixed in place. Threshold, maximal, and supramaximal intensities were determined by observing the muscle action potential on the screen of a cathode-ray oscilloscope. Action potentials were then recorded photographically while the nerve was stimulated supramaximally at frequencies of 3, 10, and 25 cps. An interval of two minutes was allowed between each volley. On two patients with myasthenia gravis, records were taken before and 30 to 45 minutes after subcutaneous injection of 1.5 mg. of neostigmine methylsulfate (prostigmin®) [4] and 0.6 mg. of atropine sulfate. The electrodes were undisturbed during the interval between the two recordings.

MEASUREMENT OF RECORDS

It is difficult to compare absolute values for potentials in different muscles and in different patients because a variety of physical and physiological factors modify the potential recorded. However, the characteristic feature of the electromyogram of patients with myasthenia gravis is a progressive decrease in amplitude of successive summated action potentials upon repetitive stimulation of the motor nerve.[5] For the purpose of this study, therefore, we thought it satisfactory to calculate the ratio of the amplitude of the negative phase of successive potentials to the amplitude of the initial potential and to assume that all factors remained constant over a period of the few seconds required for any given frequency of stimulation. In Tables 1 to 3, a ratio of less than 1.00 indicates that the amplitude of the given potential was less than that of the initial potential. The reading error averaged 1.5% of individual spike heights; maximal errors in reading produced ratios of 0.97 or 1.03. Alterations in excess of these represent physiological or pathological changes, granted that physical factors remained constant.

RESULTS

A. Normal Subjects.—Table 1 presents the electromyographic data from the orbicularis oculi muscle of three normal subjects; the accompanying figure shows a typical record from a normal subject. The amplitude of the negative phase of the initial action potential (0.8 to 1.8 mv.) following supramaximal stimulation of the motor nerve is less than that recorded by us from the adductor pollicis brevis (10.0 mv., S. D. = ± 2.1; 13 subjects), using similar electrodes. Since the amplitude of the potential recorded by this technique is considered to be proportional to the number of contracting fibers,[1] the orbicularis oculi, with fewer muscle fibers, would be expected to produce a smaller potential. Comparison with other muscle groups cannot be made because of differences in technique employed by various investigators.[6]

4. Dr. E. L. Severinghaus, Director of Clinical Research, Hoffmann-LaRoche, Inc., Nutley, N. J., supplied the drug.

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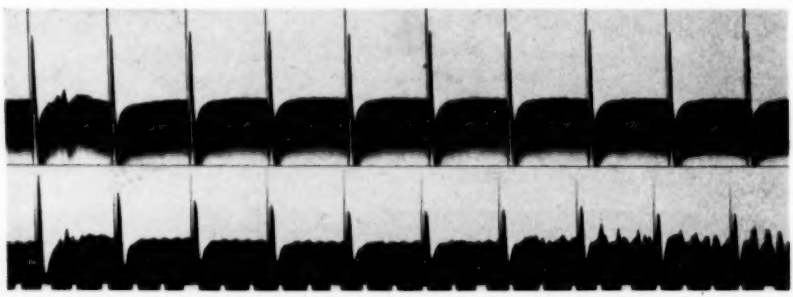
6. Harvey and Masland.[1] Hodes, Larrabee, and German.[3]

The results of the present study do not permit inferences regarding the duration of the spike potential of a single contracting fiber, nor do they give accurate information regarding the duration of negative and positive after-potentials in the orbicularis oculi muscle. To obtain these, it would have been necessary to record from single muscle fibers. In our technique, the negative phase results from negative activity of fibers directly under the active electrode, but the positive phase is a resultant of many factors, such as the negative activity of fibers under the indifferent electrode, the positive activity of fibers under the active electrode, and positive and negative activity of fibers not directly under either electrode.[3]

TABLE 1.—*Electromyographic Data from Orbicularis Oculi Muscle in Normal Subjects*

Frequency of Stimulation	Subject	Amplitude (mv.) Potential 1	Duration (Msec.) Potentials 1	5	Ratio: Amplitude of Potentials 2-10 / Amplitude of Potential 1								
					2:1	3:1	4:1	5:1	6:1	7:1	8:1	9:1	10:1
3 cps	M	1.3	5	5	1.00	1.00	1.00	1.00	1.08	1.04	1.04	1.08	1.08
	L	1.4	5	5	1.07	1.07	1.03	1.07	1.03	1.03	1.00	1.07	1.03
	K	0.8	3	3	1.04	1.04	1.04	1.04	1.04	1.04	1.08	1.00	1.08
10 cps	M	1.3	3	4	1.00	1.04	1.04	1.04	1.04	1.08	1.04	1.00	1.00
	L	1.5	5	3	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.03
	K	0.8	3	5	1.03	1.07	1.03	1.00	1.03	1.03	1.07	1.03	1.03
25 cps	M	1.0	3	4	1.00	1.00	1.10	1.10	1.10	1.15	1.15	1.15	1.15
	L	1.6	5	4	0.94	1.10	0.94	0.97	0.97	0.97	0.94	0.94	0.97
	K	1.8	3	3	0.96	1.10	1.26	1.18	1.33	1.18	1.18	1.33	1.18



Upper record: Electromyogram from normal subject (K). Stimulation rate, 10 cps; amplitude, 0.059 mv. per millimeter.

Lower record: Electromyogram from patient (D) with myasthenia gravis. Stimulation rate, 10 cps; amplitude, 0.125 mv. per millimeter. Note progressive decline in amplitude of the first to the fifth potential.

In both records the initial negative (upward) deflection is a stimulus artifact, and the time signal is at 0.04-second intervals.

The duration of the negative phase of the summated action potential from the orbicularis oculi can be measured. In our studies, it varied from 3 to 5 milliseconds, which is approximately the same duration as that recorded by a similar technique from the adductor pollicis brevis (4.4 msec., S. D. = ± 0.7; 9 subjects). The duration of the negative phase of the summated action potential is believed to be largely a measure of temporal dispersion.[3] Consequently, our measurements of duration do not permit any further conclusion than that the degree of temporal dispersion is similar in these two muscles.

The amplitudes of the 2d to the 10th potentials did not differ markedly from that of the initial potential when the nerve was stimulated at frequencies of 3 and 10 cps. At a frequency of 25 cps the ratios varied more; this may be explained in part by the discomfort produced and the consequent movement and instability of the base line. In general the orbicularis oculi reacts similarly to the muscles of the hands in that the amplitude of the summated potential is well maintained during repetitive stimulation of the motor nerve. Harvey and Masland, studying the abductor digiti quinti, noted that the second response often exceeded the first by as much as 5% at frequencies faster than 20 cps, but that it was always within 2% of the first at slower frequencies. Although we noted greater variation in records from the orbicularis oculi, there was a tendency for higher ratios to occur at frequencies of 25 cps.

B. Patients with Myasthenia Gravis.—Four patients were studied; all had clinical evidence of weakness of the facial muscles, though only two (D and C) had weakness of muscles of the hands. Electromyographic data are presented in Table 2 and in the figure.

The amplitude of the initial action potential did not differ appreciably from that of the potential recorded from the same muscle in normal subjects except in patient C, whose potential was higher than any in either group. The initial potential appears to remain normal until pronounced neuromuscular block develops, as judged from studies on other muscles in patients with myasthenia gravis [7] and on muscles in normal subjects given progressively increasing doses of curare.

We were unable to make accurate measurements of the duration of the summated negative potentials in these four patients because a fast camera speed was not available at the time.

Measurement of the amplitudes of a train of potentials showed the sharp decline characteristic of the electromyogram obtained from other muscle groups in patients with myasthenia gravis. For our four patients, the lowest ratios were 0.44, 0.53, 0.63, and 0.67. The smallest amplitude was recorded between the 3d and the 6th potential except in two instances; in these the 9th and 10th potentials were the smallest. In patient D, the ratio was lowered approximately the same amount regardless of the frequency of stimulation. In patient K, the ratios were lower when frequencies of 25 cps were used. Patient W differed from the others in that the amplitude did not decline consistently until the fourth to the sixth contraction. Her ratio of 1.13 for the amplitudes of the second and first potentials at a frequency of 3 cps is suggestive of the facilitation noted by Harvey and associates,[8] but this was not present at the faster rates of stimulation, as would be expected.

Table 2 includes the ratio of amplitudes of the fifth and first potentials obtained by a similar technique from the abductor digiti quinti muscle in the same patients. Patient C, who had weakness of both facial and hand muscles, had electromyograms characteristic of myasthenia in both groups. Patient D, who also had clinical evidence of weakness in both muscle groups, showed a highly characteristic electromyogram from the orbicularis oculi, but not from the abductor digiti quinti. The

7. Botelho, Deaterly.[2] Harvey and Masland.[5]

8. Harvey, A. M.; Lilienthal, J. L., Jr., and Talbot, S. A.: Observations on the Nature of Myasthenia Gravis: Phenomena of Facilitation and Depression of Neuromuscular Transmission, Bull. Johns Hopkins Hosp. **69**:547-565 (Dec.) 1941.

other two patients, who had weakness only of the facial muscles, had normal electromyograms from the abductor digiti quinti and the typical alterations in records from the orbicularis oculi.

C. Patients with Myasthenia Gravis Treated with Neostigmine.—Table 3 shows the effects of neostigmine methylsulfate upon the electromyogram obtained from the orbicularis oculi. The amplitude of the initial potential was not altered in patient K and was decreased slightly in patient D. (This decrease might have

TABLE 2.—*Electromyographic Data from Orbicularis Oculi and Abductor Digiti Quinti Muscles in Patients with Myasthenia Gravis Before Administration of Neostigmine*

Frequency of Stimulation	Patient*	Amplitude (mv.) Potential 1	Orbicularis Oculi Amplitude of Potentials 2-10 / Amplitude of Potential 1 Ratio: 2:1	3:1	4:1	5:1	6:1	7:1	8:1	9:1	10:1	Abductor Digiti V Amp. Pot. 1 / Amp. Pot. 2
3 cps	D	2.1	0.70	0.61	0.52	0.48	0.52	0.52	0.52	0.52	0.57	0.95
	K	1.8	0.93	0.80	0.80	0.80	0.93	0.80	0.93	0.93	0.80	1.00
	W	0.8	1.13	1.00	0.75	0.75	0.75	0.87	0.75	0.63	0.87	1.11
	C	5.4	0.89	0.78	0.70	0.67	....	....	....	....	....	0.86
10 cps	D	2.1	0.61	0.57	0.52	0.48	0.48	0.48	0.52	0.48	0.44	1.03
	K	1.8	0.93	0.87	0.80	0.80	0.80	0.80	0.80	0.80	0.80	1.05
	W	0.6	1.00	1.00	1.00	1.00	0.83	1.00	0.83	1.00	0.83	1.00
	C	...	....	....	....	....	....	....	....	....	....	0.79
25 cps	D	1.7	0.63	0.53	0.47	0.47	0.53	0.53	0.58	0.63	0.63	0.94
	K	1.8	0.73	0.67	0.67	0.67	0.53	0.67	0.60	0.60	0.60	1.00
	W	1.0	0.90	1.00	1.00	0.80	0.80	0.80	0.80	0.90	0.80	1.10
	C	...	....	....	....	....	....	....	....	....	....	0.79

* All four patients had weakness of the facial muscles and diplopia or ptosis of the lids; D and C had weakness of the extremities, whereas K and W did not.

TABLE 3.—*Electromyographic Data from Orbicularis Oculi in Patients with Myasthenia Gravis After Administration of Neostigmine*

Frequency of Stimulation	Patient	Amplitude (mv.) Potential 1	Ratio: Amplitude of Potentials 2-10 / Amplitude of Potential 1 2:1	3:1	4:1	5:1	6:1	7:1	8:1	9:1	10:1
3 cps	D	1.5	1.06	1.00	1.00	0.94	0.94	0.94	0.94	1.00	1.00
	K	1.8	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
10 cps	D	1.5	1.00	1.00	1.00	1.00	0.94	0.94	0.94	0.94	0.94
	K	1.8	1.00	1.08	1.00	1.00	1.00	1.00	1.00	1.00	1.00
25 cps	D	1.4	0.94	1.06	1.06	1.19	1.19	1.25	1.25	1.31	1.31
	K	1.8	1.00	0.80	0.80	0.73	0.80	0.80	0.93	0.87	0.93

resulted from increased resistance at the recording electrodes caused by drying of the electrode paste.) After the administration of neostigmine, the amplitudes of potentials 2 to 10 no longer declined when the nerve was stimulated at frequencies of 3 and 10 cps. In patient K, whose preneostigmine ratios were considerably lower at 25 cps than at 3 and 10 cps, the ratios at 25 cps improved after injection of neostigmine, though they did not return to 1.0. In patient D, after administration of neostigmine, there was a progressive increase in the ratios at 25 cps from 0.94, at the second potential, to 1.31, at the ninth potential. This suggests that facilitation of neuromuscular conduction can occur in myasthenia gravis after administration of neostigmine.

COMMENT

Experience with this small group of patients confirms the clinical observation that facial muscles of patients with myasthenia gravis may be affected earlier or more severely than those of the extremities. The electromyogram of the orbicularis oculi may be highly characteristic of neuromuscular block at a time when the electromyogram from the muscles of the hand is normal. Therefore, electromyographic studies of the orbicularis oculi may occasionally be a useful supplement to the neostigmine test in establishing a diagnosis of myasthenia gravis.

The reason for the earlier involvement of the facial muscles in myasthenia gravis and in progressive curarization than of the muscles of the extremities is not clear. It has been postulated that the increased sensitivity of certain muscles to curare may be due to the anatomical arrangements of the muscle fibers, i. e., uniformity of the size and direction of muscle fibers and of the nerve-fiber : muscle-fiber ratio, so that a relatively small decrease in excitability can block the impulse to most muscle fibers simultaneously, whereas in a muscle with fibers of a variety of sizes, directions, and innervation ratios a change in threshold might involve proportionately fewer muscle fibers.[9] Brown and Harvey, working with the extrinsic eye muscles of the cat, concluded that since these muscles have potentials of short duration, they must be composed of a small number of muscle fibers of uniform size and orientation and must have a low nerve-fiber : muscle-fiber ratio. It is possible that the orbicularis oculi, though a facial, and not an ocular, muscle is anatomically and physiologically more closely related to the extraocular muscles than to those of the hand. Petersén and Kugelberg[10] have reported that the duration of potentials of single motor units in voluntarily contracted facial muscles is shorter than that of potentials in the biceps brachii or dorsal interossei. Studies of other muscle groups affected early by curarization or by the myasthenic process have not been made.

SUMMARY

Action potentials were recorded from the orbicularis oculi muscle after supramaximal stimulation of the facial nerve in three normal subjects and in four patients with myasthenia gravis. These potentials were compared with those from the adductor pollicis brevis and the abductor digiti quinti. The electromyogram from the orbicularis oculi muscle was characteristic of myasthenia gravis for all four patients, even though the electromyogram from the muscles of the hand was normal for two. Possible reasons for these findings are discussed. It is concluded that more than one muscle group should be studied before the diagnosis of myasthenia gravis is excluded on the basis of electromyography. Neostigmine converted the electromyographic pattern of the orbicularis oculi to or toward normal in both patients with myasthenia gravis to whom it was administered.

Dr. George Gammon and Dr. Irving H. Leopold referred these patients to us for study.

9. Brown, G. L., and Harvey, A. M.: Neuro-Muscular Transmission in the Extrinsic Muscles of the Eye, J. Physiol. **99**:379-399 (March) 1941.

10. Petersén, I., and Kugelberg, E.: Duration and Form of Action Potentials in Normal Human Muscles, J. Neurol., Neurosurg. & Psychiat. **12**:124-128 (May) 1949.

EFFECTS OF HISTAMINE ON CEREBRAL HEMODYNAMICS AND METABOLISM

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HISTAMINE has been used extensively as a therapeutic agent in the treatment of many neurological disturbances. Its application has been based upon the hope that, since the drug is a potent peripheral vasodilator, benefit might be obtained if its action upon the cerebral vessel were similar to that observed on vessels elsewhere in the body. Animal studies by Forbes and associates [1] demonstrated that the intravenous injection of histamine was accompanied by dilatation of the pial arteries unless they were already maximally dilated as the result of ether anesthesia. Weiss and Lennox [2] believed they had demonstrated, by a reduction of the cerebral arteriovenous oxygen difference, an increase in the rate of cerebral blood flow during intravenous administration of histamine. With newer techniques now available for examination of cerebral metabolism and hemodynamics, it was considered worth while to reinvestigate the effects on the brain of intravenous administration of histamine. Moreover, in view of the wide interest in clinical applicability of the drug, it was felt to be important that its effects on already abnormal cerebral functions be considered.

METHOD

The cerebral blood flow, oxygen consumption, and vascular resistance were determined in eight hospital patients by Scheinberg's [3] modification of the nitrous-oxide technique of Kety and Schmidt.[4] After a 15-minute rest period, histamine phosphate U. S. P. ("histamine diphosphate") (0.00055%) was administered by intravenous infusion at such a rate that the mean

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This work was supported by a grant from the Abbott Laboratories, North Chicago, Ill., and by a research grant from the National Heart Institute, U. S. Public Health Service.

1. Forbes, H. S.; Wolff, H. G., and Cobb, S.: The Cerebral Circulation: X. The Action of Histamine, Am. J. Physiol. **89**:266-272 (July) 1929.

2. Weiss, S., and Lennox, W. G.: The Cerebral Circulation: XVII. Cerebral Blood Flow and the Vasomotor Response of the Minute Vessels of the Human Brain to Histamine, Arch. Neurol. & Psychiat. **26**:737-744 (Oct.) 1931.

3. Scheinberg, P., and Stead, E. A., Jr.: The Cerebral Blood Flow in Male Subjects as Measured by the Nitrous Oxide Technique, J. Clin. Invest. **28**:1163-1171 (Sept.) 1949.

4. Kety, S. S., and Schmidt, C. F.: The Nitrous Oxide Method for the Quantitative Determination of Cerebral Blood Flow in Man: Theory, Procedure, and Normal Values, J. Clin. Invest. **27**:476-483 (July) 1948.

arterial pressure was maintained at 5 to 50 mm. Hg below that of the immediately preceding control period. The administration of histamine phosphate U. S. P. was continued for a period of approximately 20 minutes, and then for the additional 10 minutes required for the experimental-flow determination.

RESULTS

The results are presented in the accompanying Table. It may be seen that there appeared to be no significant change in the mean of the cerebral blood flow rates of these subjects as the result of histamine administration in quantities sufficient to produce systemic vasodilatation, as evidenced by the average fall in arterial pressure. The mean values obtained were 41.9 cc. per 100 gm. brain per minute in the control phase and 44.5 cc. per 100 gm. brain per minute during histamine administration. The means of the arteriovenous oxygen differences were also essentially the same in the control and in the experimental observations. The mean cerebral oxygen consumption, the calculation of which is based upon the cerebral blood flow and

Effects of Histamine upon Cerebral Hemodynamics and Oxygen Utilization *

Case No. Subject	Age (Yr.) Sex	Diagnosis	C. B. F. C	C. B. F. E	M. B. P. C	M. B. P. E	C. V. R. C	C. V. R. E	A-V O_2 C	A-V O_2 E	C. M. R. O_2 C	C. M. R. O_2 E
1 R. D.	51 M	Cerebral cortical atrophy	32.1 47.2	37.8 48.3	74 85	65 70	2.3 1.8	1.7 1.5	6.45 4.00	6.86 4.24	2.14 1.89	2.59 2.05
2 F. L.	47 M	Postmeningitis	25.4	25.3	136	117	5.4	4.6	2.09	1.96	0.53	0.50
3 E. C.	57 M	Congestive heart failure	49.2	51.9	119	115	2.4	2.2	5.63	4.82	2.73	2.50
4 D. W.	40 F	Rheumatoid arthritis	48.6	45.5	114	100	2.4	2.2	5.37	5.91	2.61	2.69
5 A. M.	53 F	Cerebral thrombosis	29.9	41.0	104	96	3.5	2.3	6.90	6.10	2.06	2.50
6 H. B.	71 F	Cerebral thrombosis	52.6	49.6	142	100	2.7	2.0	6.25	6.71	3.29	3.33
7 E. L.	40 F	Posthypoglycemic coma	40.9	41.8	113	64	2.8	1.5	1.04	1.28	0.43	0.54
8 M. B.	52 F	Postbarbiturate poisoning	51.4	59.6	94	77	1.8	1.3	6.78	5.14	3.49	3.06
Mean			41.9	44.5	109	89	2.8	2.1	4.95	4.78	2.13	2.20

* C. B. F. indicates cerebral blood flow in cubic centimeters of blood per 100 gm. brain per minute; M. B. P., mean arterial blood pressure in millimeters of mercury; C. V. R., cerebral vascular resistance in millimeters of mercury per cubic centimeters of blood per 100 gm. brain per minute; A-V O_2, cerebral arteriovenous oxygen difference in volumes per cent; C. M. R. O_2, cerebral oxygen consumption in cubic centimeters of oxygen per 100 gm. of brain per minute. C indicates the control phase; E, the experimental phase during histamine infusion.

arteriovenous oxygen difference, thus showed no significant change. The only function which appeared to be influenced by the administration of histamine was the cerebral vascular resistance. This showed variable, but consistent, diminution in all patients and a significant mean reduction, from 2.8 mm. Hg per cubic centimeter of blood per 100 gm. brain per minute to 2.1 mm. Hg per cubic centimeter of blood per 100 gm. brain per minute.

COMMENT

The values for cerebral blood flow and metabolism are lower in this series than those cited by Kety and Schmidt [4] and Scheinberg and Stead.[3] However, in our laboratory,[5] we have observed a definite tendency among unselected patients for these values to decrease with advancing age. The figures reported in the present study are comparable to those for unselected patients of the same age range.

5. Fazekas, J. F.; Alman, R. W., and Bessman, A. N.: Cerebral Physiology of the Aged, Am. J. M. Sc., to be published.

There has been no evidence to indicate that histamine, at least in low concentrations, has any demonstrable influence upon cerebral enzymatic activity. It should not be surprising, therefore, that we were unable to demonstrate any mean effect upon cerebral oxygen utilization. The changes in oxygen uptake noted in individual cases were insignificant or within the limits of experimental error of the method.

The results of the nitrous oxide determinations of the cerebral blood flow, as previously stated, unequivocally indicate an absence of significant effect of histamine in accelerating the over-all cerebral blood flow. This is supported by the absence of significant mean change in arteriovenous oxygen difference in our studies. Recalculation of the data presented by Weiss and Lennox [2] reveals a mean diminution in the cerebral arteriovenous oxygen difference during histamine infusion. However, of the seven determinations in which this calculation was possible, there was no significant change in three, an apparently significant rise in two, and a very marked fall in two. The drop in the last two cases, the chief cause of the comparatively small reduction of the mean value during histamine infusion, was so extreme as to suggest admixture of highly oxygenated blood from the common facial vein with that of the internal jugular vein.

The reduction in cerebral vascular resistance noted in our series during histamine infusion tends to support the visual observations of Forbes and associates,[1] who demonstrated pial vasodilatation after parenteral histamine administration, and also the conclusion of Weiss and Lennox (cited by Forbes [1]) that dilatation of the deeper vessels was indicated by an increase in cerebrospinal fluid pressure during histamine infusion. In our cases, dilatation appeared to compensate exactly for the reduced mean arterial blood pressure, so that there was no significant alteration in cerebral blood flow. It must be recognized that this cerebral vasodilatation need not have been a direct effect of histamine action, but may have been caused by normal compensatory mechanisms acting in response to a reduction in peripheral blood pressure. Finally, it must be realized that the experimental method employed measures only the average blood flow and oxygen uptake of the entire brain and cannot detect local changes if they are small or if they are accompanied by fully compensatory reciprocal changes elsewhere in the brain.

SUMMARY AND CONCLUSIONS

Cerebral hemodynamics and oxygen uptake were studied in eight subjects before and during infusion of histamine phosphate U. S. P. ("histamine diphosphate").

The cerebral blood flow and oxygen utilization were not significantly influenced by histamine; cerebral vascular resistance was moderately reduced, indicating some dilatation of the cerebral vasculature.

The absence of change in cerebral blood flow indicates a lack of specific sensitivity to histamine on the part of the cerebral vessels; either these vessels respond to the same degree as do those elsewhere in the body, thus accepting their normal proportion of the cardiac output, or their own activity can compensate exactly for minor reductions in arterial blood pressure.

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ELECTRICAL RECORDINGS OF NORMAL AND ABNORMAL EYE MOVEMENTS MODIFIED BY DRUGS

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MOST DESCRIPTIONS of eye movements are based on direct observation. The unaided eye, however, cannot always discriminate the to-and-fro ocular movements which occur in nystagmus. Moreover, verbal description, no matter how elaborate, cannot convey the subtle character of some of these ocular excursions, particularly their frequency. For an accurate description, the eye movements must be graphically recorded.

Recordings of eye movements have been made for many years. Most of the methods, however, are cumbersome, complicated, or uncomfortable for the patient, and they do not lend themselves readily to clinical research. A method which is easy and needs only equipment ordinarily available in a hospital is one based on electrical recording.

The purpose of this study is to describe eye movements, particularly those of nystagmus, by means of electrical recording. Normal and abnormal eye movements have been studied. Furthermore, since it is known that intravenous injections of barbiturates influence eye movements and nystagmus,[1] the effect of amobarbital sodium (sodium amytal*) on all our subjects was investigated.

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From the Departments of Neurology and Psychiatry, New York University College of Medicine, and the Neurologic and Psychiatric Services of Bellevue Hospital.

This investigation was aided (in part) by a grant from the National Multiple Sclerosis Society and (in part) by a Grant-in-Aid from the United States Public Health Service, National Institutes of Health MH-139.

1. (*a*) Bender, M. B.: Effects of Barbiturates on Ocular Movements (Nystagmus), Confinia neurol. **7**:144-147, 1946. (*b*) Bender, M. B., and O'Brien, F. H.: Influence of Barbiturates on Various Forms of Nystagmus, Am. J. Ophth. **29**:1541-1552, 1946. (*c*) Bender, M. B., and Brown, C. A.: Character of Nystagmus Induced by Amytal in Chronic Alcoholics, ibid. **31**:825-828, 1948. (*d*) Bender, M. B., and Gorman, W. F.: Vertical Nystagmus on Direct Forward Gaze with Vertical Oscillopsia, ibid. **32**:967-972, 1949. (*e*) Bender, M. B.; Nathanson, M., and Green, M.: Effects of Intravenous Tolserol on Normal and Abnormal Ocular Movements, ibid. **34**:579-584, 1951.

METHOD

The technique we used is a modification of the one described by Lyman [2] in 1941. This, in turn, was based on the previous studies of several other investigators.[3] Seven solder disk electrodes are fixed to the skin with cellophane® tape, with the use of electrode jelly. Six are placed at the margins of the orbits, and one is placed on the bridge of the nose (Fig. 1). These leads are connected with the input of a conventional electroencephalograph. The machine is then operated, with some modifications, in the usual way. A four-channel recording is made, as follows:

Channel 1: Right eye. The superior-inferior electrodes record vertical movement.

Channel 2: Left eye. The superior-inferior electrodes record vertical movement.

Channel 3: Right eye. The lateral-nose electrodes record horizontal movement.

Channel 4: Left eye. The lateral-nose electrodes record horizontal movement.

With these connections, the polarities are adjusted so that in recordings of vertical movement there are an upward deflection for upward movement and a downward deflection for downward movement. In the horizontal recordings, a right lateral movement results in an upward deflection, and a left lateral movement, in a downward deflection (Fig. 2).

Fig. 1.—Placement of electrodes. The solder disks are affixed to the skin as shown with cellophane® tape, electrode jelly being used for contact. In straight-forward gaze, the pupil lies in the line between corresponding electrodes. The wires run to a conventional electroencephalograph junction box. Skin resistances measure from 3,000 to 10,000 ohms. For records of vertical movement, potentials are derived from the electrodes at the upper and lower borders of the orbits (Channels 1 and 2, Fig. 2). For horizontal movements, the electrodes at the outer canthus and on the bridge of the nose are used (Channels 3 and 4, Fig. 2).

It has been shown [4] that because amplifiers of this type (capacitance-coupled) pick up only changes in potential, these deflections represent only a change in the position of the eyes, and

2. Lyman, R. S.: Eye Movements in the Electroencephalogram, Bull. Johns Hopkins Hosp. **18**:1-31, 1941.

3. (*a*) Schott, E.: Über die Registrierung des Nystagmus und anderen Augenbewegungen vermittels des Saitengalvanometers, Deutsches Arch. klin. Med. **140**:79-90, 1922. (*b*) Meyers, I. L.: Electronystagmography: A Graphic Study of the Action Currents in Nystagmus, Arch. Neurol. & Psychiat. **21**:901-918 (April) 1929. (*c*) Fenn, W. O., and Hursh, J. B.: Movements of the Eyes When the Lids Are Closed, Am. J. Physiol. **118**:8-14, 1937. (*d*) Hoffman, A. C.; Wellman, B., and Carmichael, L.: A Quantitative Comparison of the Electrical and Photographic Techniques of Eye Movement Recording, J. Exper. Psychol. **24**:40-53, 1939. (*e*) Halstead, W. C.: A Method for the Quantitative Recording of Eye Movements, J. Psychol. **6**:177-180, 1938.

4. Powsner, E. R., and Lion, K. S.: Testing Eye Muscles, Electronics, March, 1950.

not their stationary location. Thus, even though ocular deviation is maintained, the pens return to the base line and remain there until the eye moves again. By extension, it can be shown that the amplitude of the deflection represents the velocity of the eye movement, and the shape of the individual deflection, the acceleration. Therefore, a large deflection represents a rapid movement; a sharp rise from the base line indicates a rapid change of position, and vice versa. Inspection of the records will clarify these points.

The paper was run at a speed of 1.5 cm. per second, half the usual electroencephalographic speed. Calibration was effected in two ways: first, by equalizing the actual tracings of movements, and, second, by the standard method of putting equal signals into comparable channels. Usually these two methods produced the same calibration without further adjustment. Filters were used in order to attenuate such fast potentials as muscle discharges and brain waves and to accentuate the low frequencies which constitute the usual eye-movement records.

Recordings were made while the patient executed the following eye movements, either on command or in pursuit of an object: (*a*) right and left lateral gaze, (*b*) upward and downward gaze, and (*c*) convergence and divergence. Tracings were also made of (*a*) nystagmus

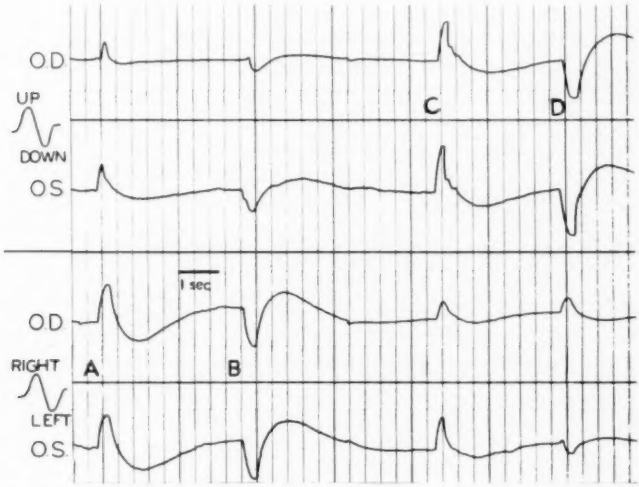

Fig. 2.—Standard gaze movements in a normal subject, as seen in the conventional four-channel record. The upper channels record vertical movement in the right and left eyes, respectively; the lower channels, horizontal movement. The direction of the deflections corresponding to the different movements is shown at the left. At *A*, the patient maintains gaze to the right; at *B*, to the left; at *C*, up, and at *D*, down. Note that the pen returns to the base line immediately, even though gaze is being maintained, showing that only change of position affects the record. The notches seen here in the descending waves in the upper channels at *C* are common in normal subjects, as is the difference in the shape of the "up" and "down" deflections.

induced by a revolving striped cylinder (opticomotor drum), the so-called opticomotor, or optokinetic, nystagmus; (*b*) nystagmus induced by caloric stimulation of the ears, (*c*) nystagmus induced by intravenous injections of 2.5% amobarbital sodium and 2% mephenesin (tolserol*), and (*d*) nystagmus of congenital or acquired types. Most of the subjects were studied before and after administration of amobarbital sodium. Various amounts of drug were given, the injection being continued until nystagmus or other alterations appeared (in one to four minutes, depending on the speed of the injection and the state of the subject). The drug was administered at the rate of approximately 100 mg. per minute, but the rate was not held constant in the same patient or consistent from one patient to another. It was necessary to find an amount which produced definite changes in eye movements, but which was insufficient to cause

drowsiness or other mental states interfering with full cooperation. Generally speaking, patients with disease of the brain tolerated smaller amounts than normal persons, although there was great variability among subjects. At intervals during and after the injection, the patient was given tests of calculation and orientation. These the patient did well, so that the effects on the eye movements could not be ascribed simply to poor cooperation or inability to understand the directions. Observations were continued for varying periods in each case in order to record the waning effects of the drug and the return to the preinjection characteristics.

MATERIALS

The subjects comprised two groups: (1) persons without evidence of organic disease of the central nervous system (members of the staff, medical students, and patients with psychiatric disorders), and (2) patients with congenital nystagmus or nystagmus due to disease of the brain.

RESULTS

Normal Subjects.—A. Normal Eye Movements: 1. Straight, forward gaze: The electrographic record of a subject looking straight ahead was essentially flat. This was not unexpected, since there was no obvious change in position of the eyes. Occasionally there were slight random deflections.

2. Vertical gaze: On the subject's looking upward (Fig. 2*C*), a fairly smooth upward deflection occurred, the pen quickly returning to the base line, even though the eye remained elevated. This deflection was equal in the two eyes. On downward gaze (Fig. 2*D*), the deflection was roughly the same but was directed downward. Sometimes one or two notches were superimposed upon some part of the deflection, as shown in *C*. Though equal in the two eyes, the deflections on downward gaze did not usually have the same characteristics as those on upward gaze in the same patient. The appearance of the deflections on upward or downward gaze varied somewhat from patient to patient and in the same subject from time to time.[5]

3. Lateral gaze: On gaze to the right (Fig. 2*A*), an upward deflection was recorded from both eyes in the "horizontal" channels. These deflections were often unequal in size in the two eyes. This difference probably represented actual variations in the velocity or amplitude of the individual ocular excursions (rather than artifacts), since they were often evident on gross inspection. Again, the pen returned to the base line, even though the eyes remained in a deviated position. Notching sometimes occurred in some part of the deflection.

On gaze to the left (Fig. 2*B*), there was a downward deflection, which was otherwise identical with the deflection on gaze to the right. Notching in one direction and not in the other was sometimes seen. As in vertical gaze, the shape and other characteristics of the waves varied considerably, even in the same patient.

4. Convergence and divergence: When the patient converged, a "converging" deflection occurred in the "horizontal" records (Fig. 3). This was because the

5. When recording was done from the four channels simultaneously, large deflections usually appeared in those pens not directly recording the particular line of gaze occurring—for example, in the "horizontal" channels (3 and 4) when the patient looked upward or in the "vertical" channels (1 and 2) when the patient looked from side to side. We were able to show, by measurements of photographs and from the results in patients who had only one eye, that these deflections were largely artifacts, and they had to be disregarded in interpreting the records. Thus, in Figure 2, the appearance of "convergence" in channels 3 and 4 when the patient looked upward was not accompanied by actual convergence, as determined from photographs.

polarities were set in this way. The reverse, of course, took place in divergence. The characteristics of the two deflections, representing convergence and divergence, were usually different. Not all patients showed the pattern illustrated here, but those who had good convergence on gross observation did so. Some subjects performed convergence by fixing at a near point with only one eye, the other deviating simultaneously outward. The concomitant outward movement, as shown in the record, was indistinguishable from lateral conjugate deviation. Still other subjects exhibited intermediate varieties, in the form of latent heterophorias. For example, there might be an initial convergence, but in a short time only one eye fixed on the object, while the other drifted outward. The details of these observations were apparent in the records.

The convergence movements were apparently faster, and therefore resulted in sharper deflections, than divergence movements, at least under the conditions of this study.

5. Blinking: A voluntary or involuntary blink appeared in the record as a sharp upward deflection in the "vertical" channels of both eyes (Fig. 10*D*), indicating that the blink was accompanied by a rapid upward movement of the eyeballs

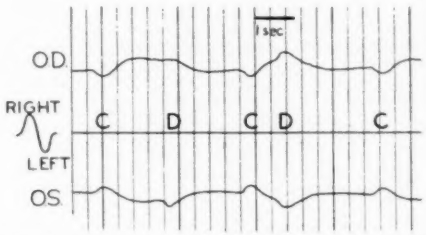

Fig. 3.—Convergence and divergence in a normal subject, shown at *C* and *D*, respectively. Recording was from "horizontal" channels only. With the arbitrary polarity setting, in which "right" corresponds to an upward deflection, the pens converge as the patient's eyes do so.

(Bell's phenomenon). The downward return movement was superimposed upon the upward deflection so soon after its onset that it usually became lost in the larger initial wave. If the patient kept his eyes closed momentarily, the deflection accompanying the opening of the lids was downward, indicating the return from the elevated position. Voluntary upward gaze produced similar deflections, but they were not so sharp and could be easily distinguished from those caused by blinks.

6. Optokinetic nystagmus: A typical response occurred when the opticomotor drum was rotated before the patient's eyes, with the instruction, "Follow the stripes" (Figs. 4*A* and 5*A*). In some cases the patient's head was within the rotating drum, so that he was surrounded by the moving stripes. There occurred a regular succession of saw-tooth waves, at frequencies related to the speed at which the drum turned. Fast and slow components of the nystagmus were shown as steep and gradual deflections, respectively. Thus, when the stripes went from the patient's right to left, the fast component was toward the patient's right; on the record the fast component showed as a steep upward ("right") deflection of the wave, followed by a more gradual downward ("left") deflection, which corresponded to the slow component. The shape and direction of the waves were reversed when the drum

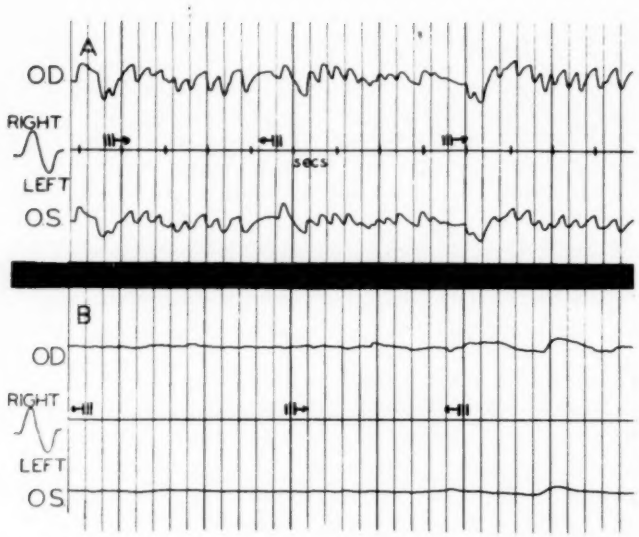

Fig. 4.—Optokinetic response in a normal subject. The stripes are moving horizontally in the directions indicated by the arrows. Recording was from "horizontal" channels only. *A*, before amobarbital sodium. When the stripes move from left to right, there are a gradually ascending ("right") deflection (slow component) and a sharply descending ("left") deflection (fast component) in each wave. The sharp, "saw-tooth" appearance is characteristic. The frequency of the waves is related to the speed of the opticomotor drum.

B, after amobarbital sodium. There is no response, and only random ocular movements are recorded.

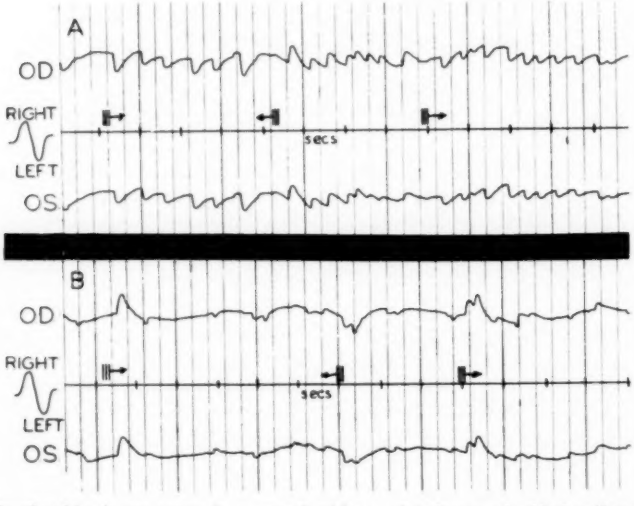

Fig. 5.—Optokinetic nystagmus in a normal subject. *A*, before amobarbital sodium (description as in Figure 4*A*).

B, after amobarbital sodium. In this type of response, as soon as the drum changes direction, there is a lateral conjugate deviation of the eyes in the direction of the stripes, and the record shows the characteristic deflection. The saw-tooth waves in the record indicate that the rapid component is in the direction of the stripes, instead of in the opposite direction, as in Figures 4*A* and 5*A*. Thus, the nystagmus recorded here is not optokinetic nystagmus, but lateral nystagmus due to the drug.

turned in the other direction. Similar waves were obtained for optokinetic nystagmus in the vertical plane. It should be noted that optokinetic nystagmus was not always present when the drum was rotated before the eyes. Optokinetic nystagmus can be decreased, and in some instances abolished, by simply telling the subject, "Look at the drum but don't follow the stripes." The change thus produced is shown in the record (Fig. 6). This decrease or disappearance of optokinetic nystagmus occurs as long as the subject makes up his mind not to took at the stripes, even though his head may be within the rotating cylinder.

7. Response to caloric stimulation: Tracings were made during cold-water irrigation of the ears, and the resulting nystagmus was recorded. Theoretically, this method of recording ocular movements could be used to distinguish the spontaneous from the induced forms of nystagmus in the same patient, as described below with respect to amobarbital nystagmus. In one patient, who had nystagmus in both directions of lateral gaze and on downward gaze, cold-water irrigation of the right ear caused augmentation of the nystagmus to the left and abolition of the spontaneous nystagmus present on right lateral gaze. Exactly the opposite occurred when the left ear was irrigated.

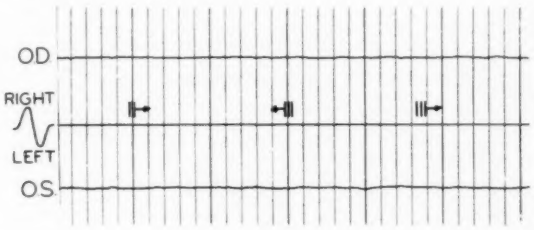

Fig. 6.—Voluntary inhibition of optokinetic response. The patient whose record appears in Figure 4 was asked to look at the drum but not to follow the stripes. There was no nystagmus.

Our material on this point is still incomplete.

B. Effect of Amobarbital Sodium: Intravenous injections of 0.1 to 0.5 gm. of amobarbital sodium in normal subjects resulted in alteration of the usual pattern of eye movements, as follows:

1. Soon after the injection was begun (usually within a minute, at an injection rate of 100 mg. per minute), its effects appeared as a nondescript disorganization of the "base line." The eyes showed random movements, and the subject could not maintain his previously good fixation. Thus, with the eyes at rest or in straightforward gaze, a record which was flat became slightly irregular soon after amobarbital sodium was injected.

2. Intravenous injection of amobarbital sodium produced nystagmus when the eyes were deviated from the midposition. This nystagmus, which occurred on vertical or horizontal deviation of the eyes, varied in character and frequency, and several frequencies often occurred simultaneously. Such combinations of frequencies are difficult or impossible to determine on gross inspection. The usual nystagmus was jerking in character, and on the record appeared as saw-tooth waves with a frequency of 1.5 to 3 per second. The fast (steep) component was in the direction of gaze. Moreover, the induced amobarbital-sodium nystagmus was usually differ-

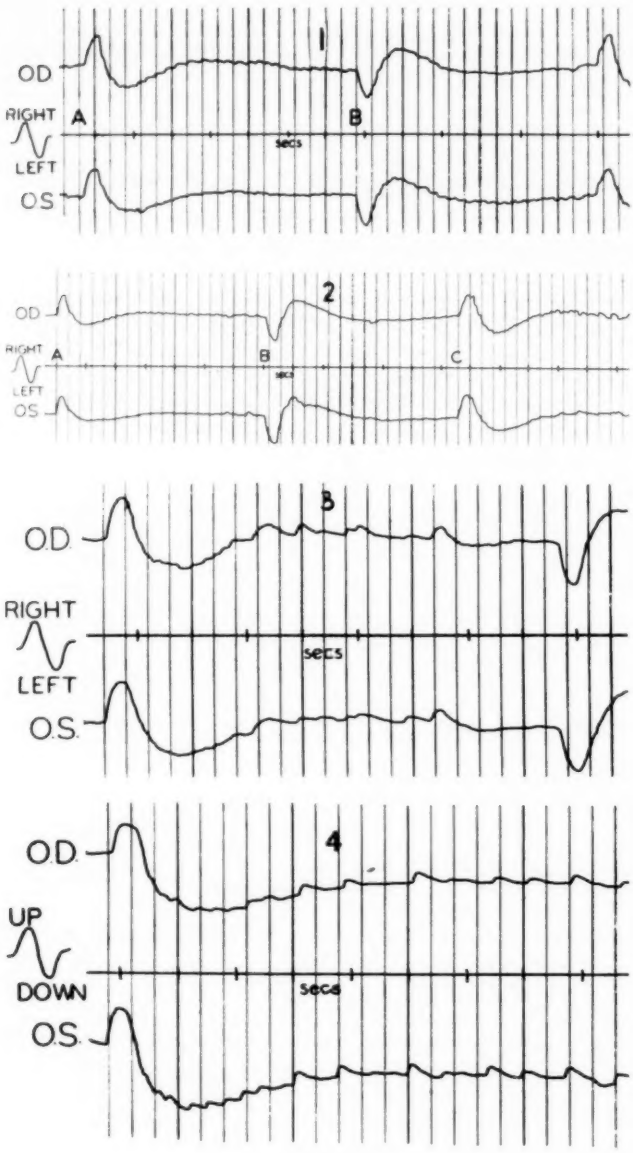

Figure 7

(See legends on opposite page)

ent in the two eyes, showing a more conspicuous movement in the abducted eye (Fig. 7,*1*). Combinations of frequencies were common, and the illustrations show records with simultaneous 2-, 4-, and 6-per-second waves (Fig. 7,*2*); 1.5- and 7.5-per-second waves (Fig. 7,*3*), and 1- and 3-per-second waves (Fig. 7,*4*). In the usual case, the movement at first gave rise to the faster frequencies, with the slower waves superimposed later. These combinations could not readily be seen with the unaided eye. The nystagmus in the vertical plane also showed differences. A prominent feature was that the nystagmus was much more prevalent and more pronounced on upward gaze. Nystagmus on downward gaze was usually absent or minimal.

3. A reduction in the velocity of the gaze movements and blinking occurred regularly. This was seen as a decrease in the amplitude of the individual deflections, the blinking deflections showing the reduced velocity very clearly. They regained their original size when the effect of the drug had worn off.

4. There was abolition of optokinetic nystagmus in all subjects after intravenous administration of amobarbital sodium, even though the subjects continued to watch the stripes. The resulting records took one of two distinct forms: In the first, there was no eye movement, and the record was flat or almost so (Fig. 4*B*). In the second, there was nystagmus when the patient looked at the moving stripes. However, it was apparent from the record that the nystagmus had the characteristics of that produced by amobarbital sodium, and not that induced by opticomotor stimulation. Such a record (Fig. 5*B*) shows clearly that the patient looked to one side, probably to the edge of the drum toward which the stripes were moving, and the resulting nystagmus was only that expected on lateral gaze as a result of administration of the amobarbital sodium. The fast component was in the direction of gaze, whereas in normal optokinetic nystagmus it is opposite the direction of rotation of the drum. The nystagmus was irregular, in contrast to the normal, in which the nystagmus is regular and proportional to the speed of the drum. Moreover, there was a deflection corresponding to lateral conjugate gaze, whereas normally it is absent. A comparison with this patient's preinjection record (Fig. 5*A*) makes these differences obvious.

EXPLANATION OF FIGURE 7

Fig. 7.—*1*, nystagmus after injection of amobarbital sodium, normal subject. At *A*, the patient looks to the right; at *B*, to the left. There is a succession of saw-tooth waves at 3 per second, with the sharp deflection (fast component) in the direction of gaze. The nystagmus is more pronounced in the abducted eye (right eye in *A*; left eye in *B*).

2, nystagmus after injection of amobarbital sodium, normal subject. At *A* and *C*, the patient looks to the right; at *B*, to the left. At *A*, there are saw-tooth waves at 4 per second. At *B*, there are large saw-tooth waves at 2 per second and smaller waves at 6 per second. The superimposition of many notches on the main deflection, at *C*, with a frequency the same as that of nystagmus, occurs only in abnormal subjects or in normal persons after administration of amobarbital sodium, and is not the same as the "physiological" notching described in the text and illustrated in Figure 2.

3, nystagmus after injection of amobarbital sodium, normal subject. Recording was from "horizontal" channels only. On right lateral gaze, two superimposed frequencies are seen: coarse waves, at 1.5 per second, and fine, regular runs, at 7.5 per second. In both types the sharp ("fast") component is in the direction of gaze.

4, nystagmus after injection of amobarbital sodium, normal subject. Recording was from "vertical" channels only. As the patient looks upward, there are coarse, saw-tooth deflections, at 1 per second, and a sequence of fine waves, at 3 per second.

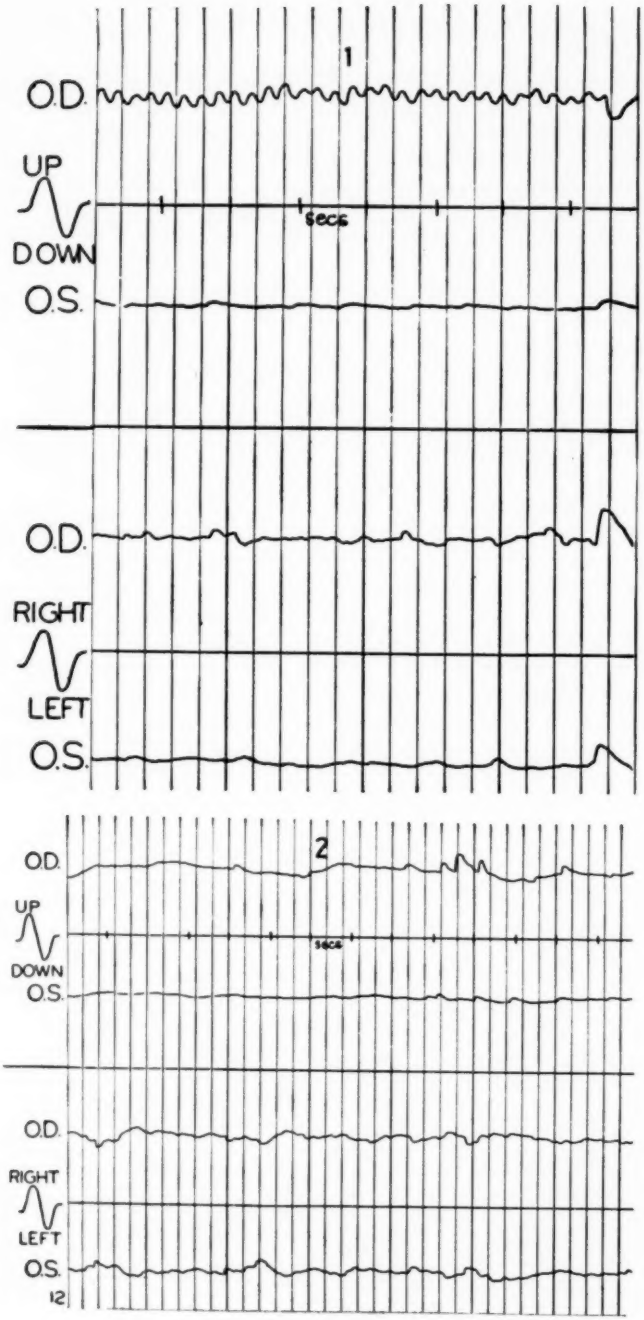

Figure 8

(See legends on opposite page)

5. Convergence was altered by amobarbital sodium. If the patient had a normal response before use of amobarbital sodium ("converging" deflections), he showed no response at all or one of the variants mentioned previously in the section on normal eye movement; i. e., he converged partially or entirely with one eye.

6. An early and constant finding was an increasing inability to maintain gaze positions, although the subjects were highly cooperative in other tests during the same periods.

Abnormal Subjects (with acquired or congenital nystagmus).—A. In previous communications, it was shown that if a patient manifested nystagmus on direct forward gaze, it was invariably abolished by amobarbital sodium.[6] This finding was confirmed in the present experiments. In patients with congenital nystagmus or multiple sclerosis who showed horizontal or vertical nystagmus on direct forward gaze, amobarbital sodium caused the nystagmus to disappear. The record of one of these patients is shown in Fig. 8, *1*. This patient, who had multiple sclerosis, showed an unusual form of nystagmus. Gross inspection revealed spontaneous vertical nystagmus on direct forward gaze in the right eye only. This nystagmus in the right eye remained the same in character on various directions of gaze. The record shows that this nystagmus was the same on right and on left lateral gaze. It lacked fast and slow components and occurred at a frequency of 4 cps. The sinusoidal waves on the record are characteristic of the so-called pendular nystagmus. Figure 8, *2* shows the disappearance of this nystagmus under the influence of amobarbital sodium, leaving only occasional random oscillations. Other movements after injection of amobarbital sodium resulted in the usual mixture of frequencies on right lateral gaze (Figure 13 shows frequencies of 1.5 and 7.5 per second) with dissociation in nystagmus in the two eyes. We have not seen such pronounced dissociation in our normal subjects.

Approximately 20 minutes after amobarbital sodium had been given, the earliest signs of returning fixation nystagmus were evident on the record. This was clearly present before the nystagmus was apparent on direct observation. Figure 9 shows two bursts of the former 4-cps activity, which later became continuous.

On another occasion a 2% solution of mephenesin was administered intravenously to the same patient. Similar effects were produced, although they were less marked and less constant. Fluctuations took place between the time of the abolition and the return of the nystagmus on direct forward gaze, as shown in

6. Bender.[1a] Bender and O'Brien.[1b] Bender and Gorman.[1d]

EXPLANATION OF FIGURE 8

Fig. 8.—*1*, vertical nystagmus on fixation in the right eye. A patient with multiple sclerosis exhibited pendular vertical nystagmus of the right eye on straight-forward gaze. The four-channel record shows on "vertical" leads a regular series of sinusoidal waves in the right eye only, at a frequency of 4 per second. The irregular deflections in the lower two channels represent random eye movements.

2, abolition of fixation nystagmus after administration of amobarbital sodium, in the patient whose record appears in *1*. Recording was from all channels. On straight, forward gaze the previous disturbance in the record of the right eye has disappeared, leaving only occasional jerky movements, clearly different from the patient's spontaneous nystagmus. The remainder of the record has not changed except for the random waves in the lower channels, which are more prominent.

Figure 10. In this record it can also be seen that a jerking nystagmus on upward gaze replaced the spontaneous pendular nystagmus. The amount of mephenesin needed to produce changes in eye movements was much greater than the effective dose of amobarbital sodium in the same patient.

Many of the patients with acquired fixation nystagmus complained of oscillopsia. The oscillopsia was usually described by the patient in such a way as to correlate

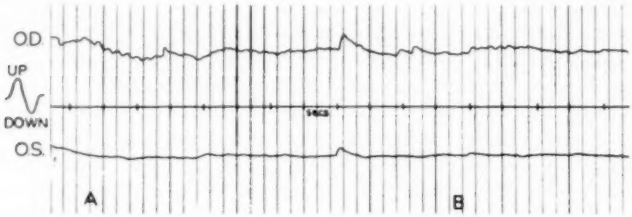

Fig. 9.—Return of fixation nystagmus after subsidence of the amobarbital-sodium effect on straight, forward gaze. Recording was from "vertical" channels only. Bursts of the former 4-per-second activity at *A* and *B* indicate return of the nystagmus in the right eye.

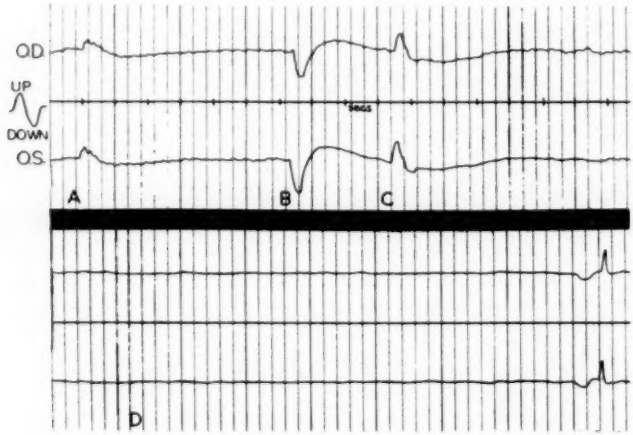

Fig. 10.—Effect of mephenesin on the patient with spontaneous nystagmus whose records appear in Figures 8 and 9. Recording was from "vertical" channels only. *A*, right lateral gaze. A succession of saw-tooth waves occurs, the steep ("fast") component being in the direction of gaze, with "pathologic" notching of the main deflection apparent.

B, left lateral gaze. There is a suggestion of irregularity in the right eye, but the waves are not of "saw-tooth" character and no notching of the main deflection occurs.

C, straight, forward gaze. The previous sinusoidal waves are present in the right eye, indicating pendular vertical nystagmus.

D, continuation of *C*, after lapse of 10 seconds. The nystagmus has disappeared. This fluctuation is characteristic of the mephenesin effect. At the far right the patient blinked and a typical deflection appeared. Note the sharp, spike-like character of the wave.

it with the observed nystagmus. Thus, a patient with vertical nystagmus described objects as "jumping up and down," whereas another, with rotary nystagmus, stated that objects seemed to follow an elliptical course. This symptom was abolished by

amobarbital sodium as soon as the nystagmus disappeared. When the influence of amobarbital sodium wore off, the oscillopsia returned, but later than the nystagmus.

A few patients with fixation nystagmus complained only of "blurring" and could not describe any feeling that objects were moving. In these patients the blurring disappeared when the nystagmus was abolished by the drug, and the patients reported great improvement in vision. This suggests that fixation nystagmus may be responsible for more instances of poor vision in multiple sclerosis than is commonly suspected, a possibility which is under investigation.

B. A differentiation of the various types of spontaneous and induced nystagmus, occurring at the same time, was possible. One patient with congenital nystagmus had nystagmus in all positions of gaze, including fixation. When the opticomotor drum was rotated before this patient's eyes, the congenital nystagmus

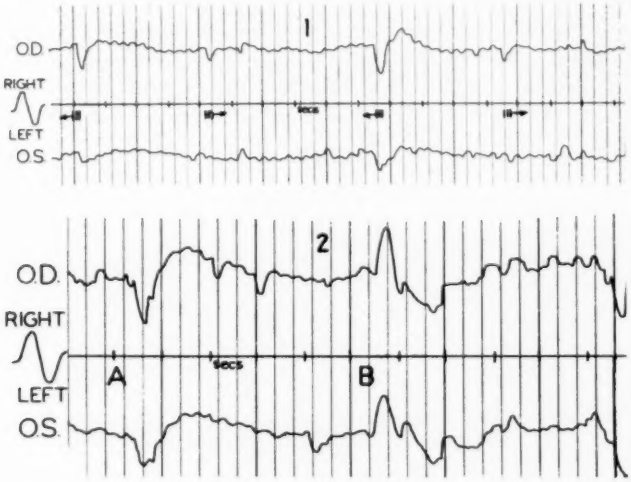

Fig. 11.—*1*, absence of optokinetic response in a patient with congenital nystagmus; recording from "horizontal" channels only. The patient had pendular nystagmus on fixation; the record shows regular sinusoidal waves at a frequency of 3 per second. The drum, turning in the directions indicated, elicited no response.

2, congenital nystagmus in the same patient whose record appears in *1*; recording from "horizontal" channels only. *A*, patient looking to left. There is a succession of sinusoidal waves at 3 per second, with occasional superimposed coarse waves at 1.5 per second.

B, patient looking to right. Fragments of three frequencies are seen—1.5, 3, and 5 per second. None of the waves are saw-toothed.

persisted, but it was evident from the record that there was actually no response to the moving stripes. All that was present was the preexisting fixation nystagmus (Fig 11, *1*). On lateral gaze, this patient showed two distinct frequencies of nystagmus, again with dissociation of the two eyes (Fig. 11, *2*). In this case, on right lateral gaze the frequencies consisted of saw-tooth waves at 1.5 per second and sinusoidal waves at 3 and 5 per second. On left lateral gaze the faster frequencies predominated. Although it could be determined grossly that there was a difference between the nystagmus on right and that on left lateral gaze, an accurate description

was possible only after inspection of the record. After this patient had received amobarbital sodium intravenously, the nystagmus changed completely in frequency and character. These changes are summarized as follows: (*a*) The nystagmus on

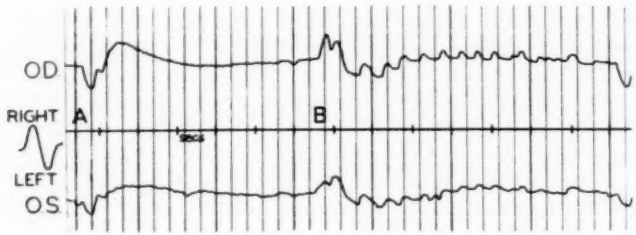

Fig. 12.—Congenital nystagmus after administration of amobarbital sodium in the patient whose record appears in Figure 11; recording from "horizontal" channels only. The nystagmus has changed completely. *A*, left lateral gaze. There is regular activity at 5 cps, without interfering frequencies.

B, right lateral gaze. There are prominent saw-tooth waves at 2 cps, with the steep ("fast") component in the direction of gaze. Remnants of the former sinusoidal, 3-per-second waves are still visible.

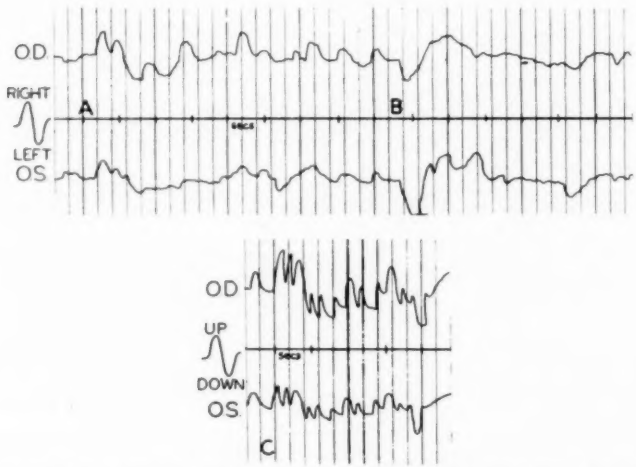

Fig. 13.—Effect of amobarbital sodium on spontaneous nystagmus in the patient whose record appears in Figures 8, 9, and 10; channels as indicated. *A*, right lateral gaze. Large, slow waves appear at a frequency of 1 per second, with some fragmentary faster activity. This is much more pronounced in the right eye, whereas the left shows chiefly the faster frequencies (especially at 7 per second).

B, left lateral gaze. The description of the two eyes given in *A* is almost exactly reversed here.

C, upward gaze. Large, saw-tooth waves appear at a frequency of 3 per second, with the sharp ("fast") component in the direction of gaze.

forward gaze and convergence was abolished. Similar effects in another patient are shown in Figure 13. (*b*) On right lateral gaze (Fig. 12) there was a jerking nystagmus (saw-tooth waves) at 2 per second, with the fast component in the

direction of gaze. This is the usual type of nystagmus seen with amobarbital sodium and did not differ from the responses of normal subjects. It could be seen, however, that the patient's spontaneous 3-per-second sinusoidal waves persisted during amobarbital sodium and were superimposed upon the record. (*c*) On left lateral gaze

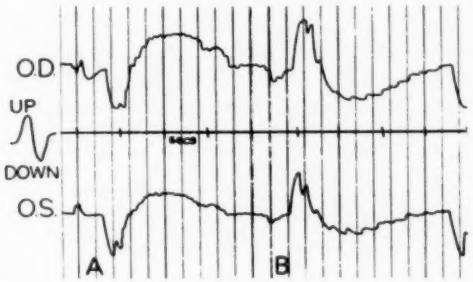

Fig. 14.—Spontaneous nystagmus in a patient with multiple sclerosis, showing nystagmus on upward and downward gaze; recording from "vertical" channels only. *A*, downward gaze: regular, sinusoidal waves at 7.5 per second.

B, upward gaze: saw-tooth waves at 3 per second, with the sharp ("fast") component in the direction of gaze. Fragments of the faster frequency are also seen on downward gaze.

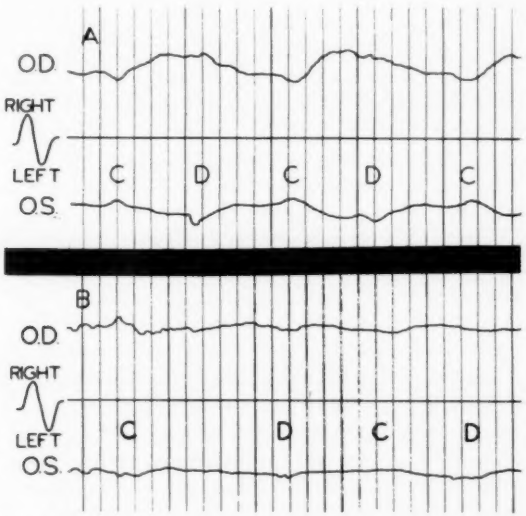

Fig. 15.—Effect of amobarbital sodium on convergence in a patient with multiple sclerosis; recording from "horizontal" channels only. Convergence and divergence are shown at *C* and *D*, respectively. *A*, before use of amobarbital sodium. Normal convergence is shown. *B*, after use of amobarbital sodium. Convergence is greatly diminished, to absence of response, with fragments of induced nystagmus.

an entirely new frequency appeared (5 per second, at a lower amplitude), and there were no other recognizable waves. This response was not seen in any of our normal subjects.

It was possible to correlate to some extent the different frequencies seen on the record with the usual descriptions of grossly observed nystagmus. Frequencies below 6 per second are ordinarily described as "coarse" nystagmus (including movements further qualified as "jerky"), whereas the movements at 7.5 per second and faster are often referred to as "shimmering."

In another patient, with multiple sclerosis, nystagmus was observed grossly to be present on upward and downward gaze. These appeared to be identical in character as seen with the naked eye. The electrical record, however, showed that there were two frequencies, one in each direction. Figure 14 shows that the nystagmus on upward gaze consisted of saw-tooth waves at a frequency of about 3 per second. When the patient looked down, however, sinusoidal waves were recorded at 7.5 per second. This patient, who showed fairly good convergence before receiving amobarbital (Fig. 15), reverted to the "lateral-gaze" type of convergence after amobarbital sodium had been given, the concomitant lateral nystagmus showing clearly in the record.

COMMENT

The effect of drugs on normal and abnormal eye movements has been investigated in the past, and gross observations on a wide variety of ocular conditions have been made.[1] Simple inspection, however, is not sufficient to detect all the varieties of extraocular movements, particularly when nystagmus is present, and verbal description is insufficient to give a clear picture of what is happening.

Other methods have been used to record nystagmus. A recent publication[7] describes these methods in some detail, and an exhaustive historical discussion is available in the work of Carmichael and Dearborn.[8] Earlier workers attached systems of levers to the closed lids, permitting them to make tracings on a smoked kymograph drum. Motion pictures have been used extensively. A record can be obtained by throwing a light beam on the surface of the eye (or on a mirror attached to a contact lens) and directing the reflection on to a photographic paper; this can be an exceedingly sensitive method and detects the finest ocular movements, including "physiological nystagmus." Unfortunately, none of these techniques is completely satisfactory for clinical research. They do not permit of publication or of otherwise easy access to others (e. g., motion pictures), are unacceptable to the subject, are cumbersome to use, or require highly specialized equipment. The records published here illustrate a method which requires equipment usually available in a hospital, is completely acceptable to the patient, even if he is bedridden, provides printable records available for general inspection, and reveals details not accessible to the unaided observer. The method provides data which can be compared with others gathered at various stages during the course of the patient's illness, with records taken during other diagnostic and therapeutic procedures, and with the records of other observers.

7. Lord, M. P., and Wright, W. D.: Investigation of Eye Movements, Report on Progress in Physics, The Physical Society, London, 1950, Vol. 13, p. 1.

8. Carmichael, L., and Dearborn, W. F.: Reading and Visual Fatigue, Boston, Houghton Mifflin Company, 1947.

This method, which in various forms has been in use since 1922,[3a] was used to study, in addition to gaze movements and nystagmus, caloric responses,[9] optokinetic nystagmus,[10] reading movements,[11] and the relation of simultaneous head and eye movements.[3c] Lyman [2] and Jung and Mittermaier [9b] studied large series of patients and described many of the patterns seen in this study. Jung and Mittermaier [9b] recorded eye movements in patients with spontaneous nystagmus and in normal subjects. They attempted to correlate the changes in response to the opticomotor drum immediately following caloric stimulation. They observed three patterns distinctive of peripheral labyrinthine disease, vestibular nuclear defects, and supranuclear lesions, respectively. Lyman [2] also proposed that this technique might be used to identify eye-movement artifacts in the electroencephalogram.

Although earlier workers in the field [12] believed that eye-muscle potentials were being recorded, experiments by Mowrer, Ruch, and Miller [13] and others [14] indicated that the corneoretinal potential was the source of the electrical energy appearing in the oscillographic record. This problem, however, does not bear directly on the present study, since it is obvious that eye movements are being recorded, whatever the underlying mechanism.

The records themselves illustrate that certain features of eye movements can be detected by this method, for example, the modification of normal movements by these drugs, the variation in response to drugs from one patient to another, the normal pattern of optokinetic nystagmus and its modification by drugs, the differentiation of various simultaneous frequencies of nystagmus in normal subjects after administration of drugs and in abnormal patients before and after the use of drugs.

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11. Carmichael and Dearborn.[8] Tinker, M. A.: Study of Eye Movements in Reading, Psychol. Bull **43**:93-120, 1946.

12. Schott.[3a] Meyers.[3b] Jacobson, E.: Electrical Measurements of Neuromuscular States During Mental Activities: III. Visual Imagination and Recollection, Am. J. Physiol. **95**:694-702, 1930.

13. Mowrer, O. H.; Ruch, T. C., and Miller, N. E.: The Corneo-Retinal Potential Difference as the Basis of the Galvanometric Method of Recording Eye Movements, Am. J. Physiol. **114**:423-428, 1936.

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The detailed analysis of certain forms of spontaneous nystagmus, particularly the dissociation of the two eyes, is possible with this technique. The method enabled us to study changes in eye movements induced by disease, drugs, or sensory stimulation. It is evident that the records are sufficiently reproducible and detailed to permit collection of accurate data.

The use of drugs made it possible to study induced, reversible changes in eye movements, both normal and pathologic. These changes, when recorded appropriately, provide useful data for neuro-ophthalmologic research and suggest further lines of investigation.

SUMMARY

The effects of the drugs amobarbital sodium and mephenesin on normal and abnormal eye movements were studied by means of electrical recordings. They may be summarized as follows: (*a*) In normal subjects these drugs produced nystagmus on lateral, upward, and downward gaze. The usual pattern was a jerky nystagmus at 1.5 to 3 cps, with the fast component in the direction of gaze. The two eyes did not respond identically on lateral gaze, nystagmus being much more pronounced in the abducted eye. Often other frequencies were present, sometimes as many as three simultaneously, varying from 4 to 10 cps. (*b*) These drugs abolished optokinetic (opticomotor) nystagmus. By means of these records it was possible to distinguish optokinetic response from the nystagmus induced by amobarbital sodium or spontaneous nystagmus. (*c*) There was an early, and almost constant, reduction in the velocity of the eye movements. After the effect of the drug had worn off, the amplitude of the movements returned to normal. (*d*) Convergence and divergence were altered after administration of amobarbital sodium. Either convergence was abolished completely, or the patient fixed the object at a near point with one eye only, the other drifting outward. (*e*) The early disorganization of the record after injection of amobarbital sodium was detected and described, as were the first signs of return to the previous state. (*f*) The patients had great difficulty in maintaining positions of gaze.

In subjects with acquired or congenital nystagmus, intravenous injection of amobarbital sodium produced the following changes: (*a*) Prompt disappearance of a preexisting nystagmus on direct forward gaze. If there was associated oscillopsia, the patient reported its disappearance. (*b*) Changes in the nystagmus on lateral and vertical gaze. Different frequencies appeared simultaneously, and these could be detected and described by means of the records. Differences between the two eyes were usually present. As in the normal group, spontaneous nystagmus, nystagmus due to amobarbital sodium, and nystagmus occurring in response to the opticomotor drum or caloric stimulation could be distinguished.

The response to mephenesin was found to be similar to that occurring after amobarbital sodium. Fluctuations were more apparent, however; the time and duration of its effects were not so constant, and a much greater amount of the drug was required to influence the eye movements.

EFFECTS OF SUBTOTAL LESIONS OF FRONTAL GRANULAR CORTEX ON DELAYED REACTION IN MONKEYS

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MANY STUDIES have shown that bilateral ablation of the frontal granular cortex in monkeys is followed by inability to perform at better than a chance level on the delayed-response test, even at delays of less than five seconds. Evidence for more precise localization of lesions within the prefrontal region which produce this symptom, however, is scant, elusive, and contradictory. In 1935 Jacobsen [1] found that after complete bilateral removal of all prefrontal cortex in the monkey except for a strip "several millimeters in width" anterior to the premotor area on one side only, the resulting deficit was quantitatively incomplete and was expressed as a shortening of the length of delay after which the animal could respond accurately. From this experiment, he suggested that the degree of deficit is inversely related to the amount of intact tissue of the frontal lobes. A similar experiment on a baboon, in which there was unilateral sparing of a band of tissue 1 cm. wide anterior to the arcuate sulcus, was reported by Jacobsen in 1936.[2] On the basis of studies of bilaterally symmetrical subtotal lesions, Jacobsen and Taylor [3] reported at the 1937 meeting of the American Psychological Association that "the portion of the frontal lobe focally concerned with delayed response consists of the extreme frontal pole and the tissue lateral to the frontal sulcus." They retained the qualification, however, that deficits following larger lesions are severer and more permanent than those following less extensive removals. The 1943 edition of Fulton's "Physiology of the Nervous System" [4] cites unpublished experiments of Jacobsen and associates as establishing that lesions of Walker's Area 8 or 9 are "without effect on delayed reaction, but that a full-blown deficit can be demonstrated after bilateral ablations of the frontal poles, i. e., areas 9b and 10." This locus does not

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This paper is based in part on a dissertation submitted to the Graduate School of Yale University in candidacy for the degree of Doctor of Philosophy.

Dr. K. S. Lashley aided in the planning and execution of the experiments. The present manuscript was prepared, after the death of the author, by Dr. Josephine Semmes.

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3. Jacobsen, C. F., and Taylor, F. V.: Behavioral Changes Associated with Lesions of the Frontal Lobes in Monkeys, Psychol. Bull. **34**:767, 1937.

4. Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1943.

fully coincide with that designated by Jacobsen and Taylor, and the characterization of the deficit as "full-blown" following a lesion of such restricted extent disagrees with Jacobsen's often-repeated conclusion that the severity of the deficit is dependent on the mass of prefrontal tissue removed. Campbell and Harlow [5] pointed out that their experiments showed that Fulton's report of Jacobsen's finding "needs considerable qualification," for after complete removal of Walker's Areas 8b, 9, 10, 11, and 46, severe damage to Areas 12 and 25, and partial invasion of Areas 8a, 13, and 45, there is minimal lasting impairment. These data also cast serious doubt on the localization favored in the report of Jacobsen and Taylor. Further study of the effects of subtotal ablations of frontal granular cortex is obviously required.

Such ablations may also provide information on the dissociability of the various symptoms reported to follow removal of cortex anterior to the precentral gyrus. These symptoms in the monkey are principally of three kinds: hyperactivity, inability to respond accurately in the delayed-response test, and disorders of visual perception. The visual changes are usually ascribed to encroachment on Area 8, whereas the other disturbances are said to depend on cortex situated rostrad. A relationship among the symptoms, however, is suggested by the facts that (*a*) the frontal eye fields, as defined by stimulation, are not confined to Area 8, but include parts of Areas 9 and 46, on the superior and middle frontal gyri,[6] and (*b*) reduced illumination eliminates hyperactivity and restores the capacity for delayed response.[7] Since the usual form of the delayed-reaction test involves memory for a visual cue, i. e., sight of the lure in a specific location in visual space, it is not clear whether the loss of the delayed response is specifically a visual defect or is one of a more general character. A test of the generality of the behavioral change following prefrontal operation would be to present a form of this problem in which the differentiating cue prior to delay is received through a sense modality other than vision.[8] Differential effects of various subtotal ablations on alternative forms of the delayed-response test might clarify both the nature and the mechanism of the observed defects.

The validity and significance of conclusions drawn from relatively small lesions within a region are dependent to an unusually great degree upon accurate specification of the removals by postmortem histological analysis and upon the use of

5. Campbell, R. J., and Harlow, H. F.: Problem Solution by Monkeys Following Bilateral Removal of the Prefrontal Areas: V. Spatial Delayed Reactions, J. Exper. Psychol. **35**:110-126, 1945.

6. Smith, W. K.: The Frontal Eye Fields, in Bucy, P. C.: The Precentral Motor Cortex, Urbana, Ill., University of Illinois Press, 1944, pp. 307-342.

7. (*a*) Kennard, M. A.; Spencer, S., and Fountain, G., Jr.: Hyperactivity in Monkeys Following Lesions of the Frontal Lobes, J. Neurophysiol. **4**:512-524, 1941. (*b*) Malmo, R. B.: Interference Factors in Delayed Response in Monkeys After Removal of Frontal Lobes, ibid. **5**:295-308, 1942.

8. It might be considered that this question has already received an adequate answer in the work of Jacobsen and Nissen (Jacobsen, C. F., and Nissen, H. W.: Studies of Cerebral Function in Primates: IV. Effects of Frontal Lobe Lesions on the Delayed Alternation Habit in Monkey, J. Comp. Psychol. **23**:101-112, 1937), who tested prefrontal monkeys on delayed alternation and found them as completely incapacitated in solution of this problem as in the usual delayed-reaction test. However, although a kinesthetic cue is available to the subjects in delayed alternation, it is not essential to correct solution; considering the dominance of vision in the primate, it seems more likely that visual cues would be used.

reliable criteria of functional division. Lashley and Clark [9] emphasized that architectonic schemata of the prefrontal region are based largely on fortuitous characters, which show much individual variation. Such charts are consequently of little value as guides in studies of cortical removals. Parcellation along lines of distinctive afferent or efferent connections has more promise of functional significance.

The general region to be investigated in the present study includes the lateral and dorsal surfaces of the frontal lobe rostral to the arcuate sulcus. This sector receives projections from the thalamic nucleus medialis dorsalis. The medial surface ventral to the cingular sulcus and the orbital surface are excluded—the former because it is part of the projection field of the anterior group of nuclei,[10] and probably related in activity more to the remainder of the limbic cortex [11]; the latter because it appears to be part of a separate system involving mainly the magnocellular portion of nucleus medialis dorsalis and the hypothalamus.[12]

The present study is concerned with effects of ablations of the superior, middle, and inferior parts of the lateral prefrontal region. Studies of resultant thalamic degeneration provide additional information on the ordering of the connections of these regions within nucleus medialis dorsalis. As indices of behavioral alteration, tests of delayed reaction to auditory, as well as visual, cues were employed.

METHODS

Subjects and Test Procedures.—Six monkeys (Macaca mulatta) were used in this experiment. Their weights ranged from 2.5 to 4.5 kg. Two (Animals 1 and 5) were males, and the others, females. None had prior experimental experience. Animals 1, 5, and 6 were tested before, and again after, operation; Animals 2, 3, and 4 received training only after operation. The preoperative scores of animals 1, 5, and 6 were combined with those of three other intact animals to give mean scores and standard deviations for each problem. These figures provide a standard of comparison for postoperative learning scores. Animal 6 and one of the latter three animals were also tested preoperatively for retention of auditory discrimination and auditory delayed response approximately six months after original training.

For the visual delayed-response tests, the subject was brought in a portable cage from his living quarters to an experimental room in another building. The cage was placed on a table behind an opaque screen and a glass window. Two inches in front of the screen and the window were two No. 1 cans, 15½ in. (38 cm.) apart. These were the containers under one or the other of which the monkey observed the food being hidden prior to delay. For the first series of tests, only the glass window separated the animal from the choice objects. A trial was given in the following way: A small piece of fruit was exposed for five seconds in front of the correct can; the can was then raised and the food placed underneath. After the appropriate delay interval, the glass window was raised and the animal allowed to make his choice. The subjects were adapted to the problem at a minimal delay interval (called 0 second), after which delays of 5, 10, 15, 20, 25, and 30 seconds were employed. After this series, the opaque screen was lowered during the delay period and between trials, and the animal was again tested at the

9. Lashley, K. S., and Clark, G.: The Cytoarchitecture of the Cerebral Cortex of Ateles: A Critical Examination of Architectonic Studies, J. Comp. Neurol. **85**:223-306, 1946.

10. Mettler, F. A.: Extracortical Connections of the Primate Frontal Cerebral Cortex: I. Thalamo-Cortical Connections, J. Comp. Neurol. **86**:95-117, 1947.

11. McCulloch, W. S.: The Functional Organization of the Cerebral Cortex, Physiol. Rev. **24**:390-407, 1944.

12. Walker, A. E.: The Medial Thalamic Nucleus: A Comparative Anatomical, Physiological and Clinical Study of Nucleus Medialis Dorsalis Thalami, J. Comp. Neurol. **73**:87-115, 1940.

same delay interval as before. Each subject was given approximately 50 trials a day and had to meet a criterion of 90% correct responses in a session at each delay interval before the next longer interval was used.

The same general situation was used for training on auditory delayed response. Preliminary to this test, the animals were taught an auditory discrimination. For both discrimination and delayed response, two identical small boxes, 14½ in. (37 cm.) apart, served as choice objects. The sounds to be discriminated were those of a buzzer and an ordinary door bell. The bell and the buzzer were about 85 in. (2 meters) apart, the bell being mounted on the wall to the left of the subject, about 6 ft. (180 cm.) away, and the buzzer, on the right side of the table. Both bell and buzzer were out of the subject's range of vision. For the discrimination problem, the correct choice box was baited behind an opaque screen; the appropriate

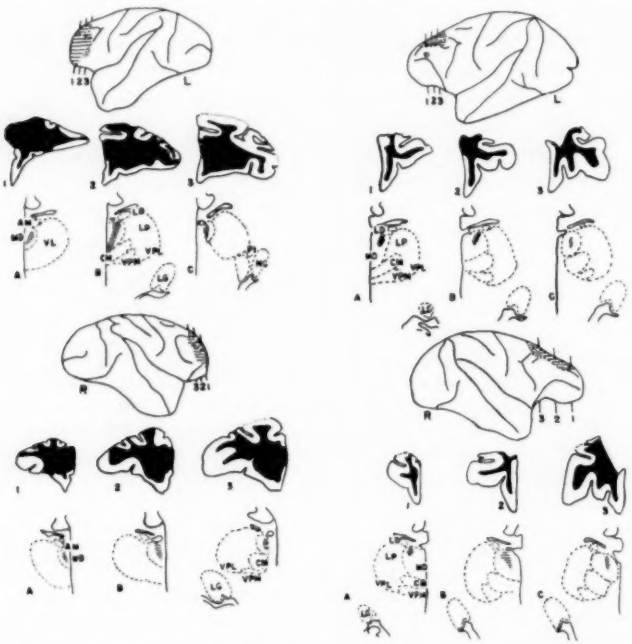

Fig. 1.—Record of lesions in Subjects 1 and 2. In this, and in the following reconstructions of cortical lesions, complete excision is indicated by hatching and partial destruction by stippling. Preservation of the depths of sulci is indicated by interrupted lines. The positions of the cross sections through the lesions are shown by the numbered lines on the surface drawings. In these cross sections the cortical gray matter is represented in white. Sections through the thalamus, from anterior to posterior, are shown for each hemisphere. Definitely degenerated regions are hatched; regions of "doubtful" degeneration are stippled. *VA*, indicates nucleus ventralis anterior; *AM*, nucleus anteromedialis; *MD*, nucleus medialis dorsalis; *VL*, nucleus ventralis lateralis; *VPL*, nucleus ventralis posterolateralis; *VPM*, nucleus ventralis posteromedialis; *LD*, nucleus lateralis dorsalis; *LP*, nucleus lateralis posterior; *CM*, centrum medianum; *PL*, nucleus pulvinaris lateralis; *PM*, nucleus pulvinaris medialis; *PI*, nucleus pulvinaris inferior; *LG*, lateral geniculate body; *MG*, medial geniculate body.

auditory stimulus was turned on for five seconds, the screen raised, and the animal allowed five additional seconds in which to make a choice with the auditory stimulus still sounding. If the choice was not made within five seconds, the screen was lowered and the trial repeated. The sound of the buzzer indicated food in the box to the right of the subject, whereas the ringing of the bell meant that the left box was correct. Mild electric shock, from the incorrect box,

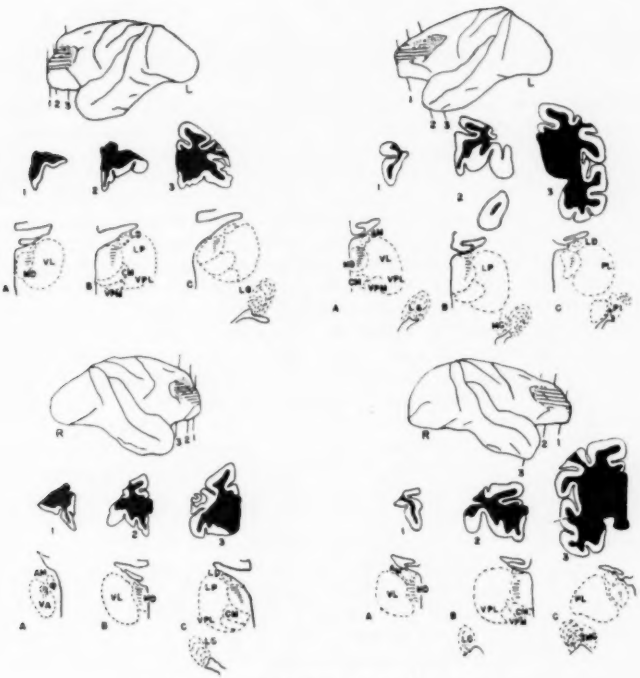

Fig. 2.—Record of lesions in Subjects 3 and 4.

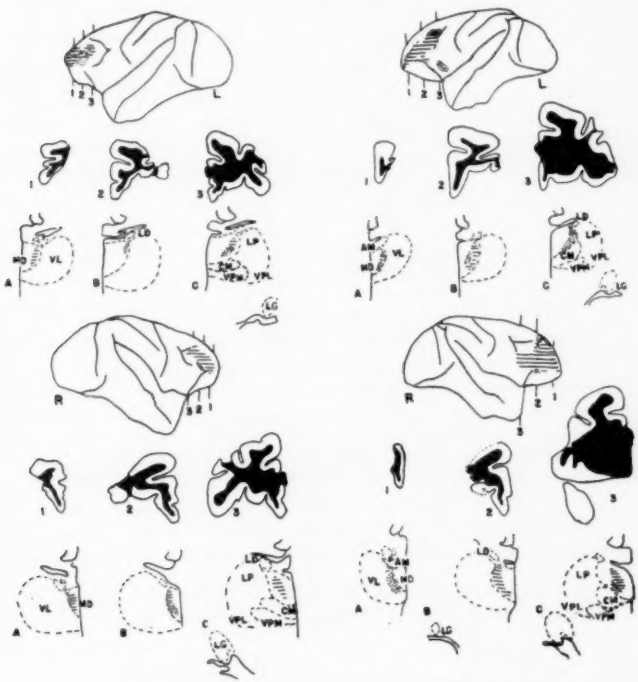

Fig. 3.—Record of lesions in Subjects 5 and 6.

was used as punishment for errors in about one-quarter of the trials. Immediate correction was allowed. Approximately 30 trials a day were given on the discrimination problem, until the subject met a criterion of 90% correct choices in a session. The procedure for the auditory delayed-response test was the same, except that the sound was turned off before the beginning of the delay interval and the screen was not raised until the delay had elapsed. No shock was used in these trials, and no correction was allowed. Delays of 0, 2½, 5, 7½, 10, and 12½ seconds were employed.

Operations.—Operations were performed with aseptic technique, using pentobarbital anesthesia. Tissue was removed in a block in the case of Subjects 1 and 2, and by aspiration in the other animals. All ablations were made bilaterally in one stage.

The operations were designed to remove the following areas: the complete prefrontal region in Animal 1; the dorsal part in Animal 2; the midlateral part in Animals 3, 4, and 5, and the ventrolateral part in Animal 6. After completion of testing the animals were killed. Reconstructions of the cortical lesions were made from serial sections, and thalamic degeneration was studied. Histological procedures, the method of reconstruction, and the criteria of retrograde degeneration have been described previously.[13] Reconstructions of the lateral surfaces of the hemispheres, representative cross sections through the lesions, and sections through the thalamus are shown in Figures 1 to 3.

RESULTS

Verification of Lesions

Animal 1 (Fig. 1).—The frontal poles were totally removed. More posteriorly, destruction was confined to the lateral surfaces, involving mainly the dorsal and midlateral parts. Considerably less of the inferior gyrus was removed, particularly on the right. The posterior boundary of the lesion was at about the level of the end of the sulcus rectus. In the thalamus, degeneration was present in nucleus medialis dorsalis, and possibly also in nucleus anteromedialis. Throughout most of nucleus medialis dorsalis there was a central zone of intense gliosis and disappearance of cells. Degeneration extended farther ventrad on the left, probably reflecting the greater damage to the inferior frontal gyrus on this side. In posterior sections, the degenerated region was confined to the medial part of the nucleus.

Animal 2 (Fig. 1).—The lesions were confined to the dorsolateral and dorsomedial parts of the prefrontal region above the sulcus rectus except for a small patch of partial damage in the left ventrolateral region. On the left, the removal extended from about the end of the sulcus rectus to a plane cutting the sulcus about one-third of the distance from its anterior tip. On the right, the region completely removed was approximately symmetrical with that on the left, but there were zones of partial damage anterior and posterior to these limits. Thalamic degeneration was clearly present only in nucleus medialis dorsalis and was more complete on the right. A dorsocentral strip of the nucleus showed these degenerative changes. Approximately the anterior one-third of this nucleus on the left showed no retrograde degeneration; on the right, degeneration reached farther anteriorly but spared the extreme anterior tip. The posterior tip of the nucleus was intact on both sides. There was questionable evidence of degeneration in nucleus anteromedialis of each thalamus.

Animal 3 (Fig. 2).—The lesion in this animal was the largest of the three midlateral removals. The frontal poles were completely removed, but posteriorly the lesions were confined to midlateral parts. Damage extended to about midway between the end of the sulcus rectus and the angle of the arcuate sulcus. In both thalami, degeneration was present throughout the length of nucleus medialis dorsalis, and possibly within nucleus ventralis anterior and nucleus anteromedialis. In nucleus medialis dorsalis, the degenerated zone was located dorsolaterally in anterior sections through the nucleus, becoming central in the middle part and finally medial in the posterior tip.

Animal 4 (Fig. 2).—The removal in this monkey was similar to that in Animal 3 except that in the left hemisphere destruction was less complete between the limbs of the arcuate sulcus. Retrograde changes in nucleus medialis dorsalis were similar to those found in Animal 3, except

13. Blum, J. S.; Chow, K. L., and Pribram, K. H.: A Behavioral Analysis of the Organization of the Parieto-Temporo-Preoccipital Cortex, J. Comp. Neurol. **93**:53-100, 1950.

that in anterior sections on the right the degenerated region occupied a more lateral and ventral position. In both thalami the entire extent of this nucleus was involved, except the extreme posterior tip. No degeneration was found in any other nucleus.

ANIMAL 5 (Fig. 3).—The midlateral removal in this animal was smaller than that in Animal 3 or Animal 4. The immediate region of the sulcus rectus was ablated. The frontal pole was completely spared on the right, and only partially damaged on the left, lateral surface. Posteriorly, almost all the tissue between the limbs of the arcuate sulcus was undamaged on the left. On the right, the ablation reached the superior limb of the arcuate sulcus but spared the adjacent inferior midlateral surface. In the left thalamus, degeneration was present only in nucleus medialis dorsalis. In anterior sections, the lateral portion showed retrograde changes; more posteriorly, only a dorsolateral patch of degeneration could be distinguished; still farther back, the whole degenerated zone had moved somewhat centrally, and there appeared to be slightly more glia and fewer cells ventrad. In successive sections of the right thalamus, also, the area of nucleus medialis dorsalis showed retrograde changes shifting from lateral to central. The posterior tip of this nucleus was not degenerated in both thalami. There was questionable degeneration in nucleus anteromedialis on the right.

ANIMAL 6 (Fig. 3).—The ablation in this animal involved predominantly the inferior frontal gyrus but extended into the midlateral region between the limbs of the arcuate sulcus on the left and into midlateral and dorsolateral regions anteriorly on the right. In the left thalamus, degeneration was confined to nucleus medialis dorsalis, involving principally the lateral and ventral parts. The degeneration faded out in the posterior tip of the nucleus. On the right, the degeneration in nucleus medialis dorsalis was approximately symmetrical in the anterior half but became more centrally located posteriorly. The extreme posterior tip was likewise intact on the right. There was a zone of degeneration in the medial part of nucleus ventralis lateralis in the right thalamus, and also possibly in nucleus anteromedialis.

EFFECTS ON BEHAVIOR

Visual Delayed Response (Tables 1 and 2).—Without Screen: After operation, no subject, except Animal 6, was able to meet the criterion of 90% correct responses at all delay periods through 30 seconds. Animals 1 and 3 failed to meet this criterion at the minimal delay (called 0 second) after operation; Animal 4 failed at 5 seconds; Animal 5, at 10 seconds, and Animal 2, at 25 seconds. However, the scores of Animals 2 and 3 were significantly above chance at the 5% level of confidence at all delays, and the score of Animal 4, at all intervals under 30 seconds. The score of Animal 5 was not significantly above chance at 25 seconds; yet a better, and significant, score was made at 30 seconds. Animal 1 was not tested above 0 second because of accidental death; his score at this delay was highly significant.

With Screen: After operation, Animal 6 was the only subject who met the criterion at all delays. Animal 2 made scores significantly above chance at all intervals under 20 seconds; Animals 3 and 4 dropped to a chance level at delays greater than 0 and 5 seconds, respectively. At all delays, the scores of Animal 5 did not differ reliably from chance.

Auditory Discrimination (Table 3).—The two monkeys who were tested for retention without an intervening operation met the criterion of 90% correct responses in the minimum possible number of trials, indicating practically perfect retention over a period of months. Two weeks after operation, retention was still perfect in Animal 6, but Animals 1 and 5 (the only other animals with preoperative training) showed only slight saving in relearning. All the animals trained only postoperatively eventually met the required criterion of learning, but were over

TABLE 1.—*Visual Delayed-Response Scores for a Group of Six Normal Monkeys* *

	Period of Delay, Sec.						
	0	5	10	15	20	25	30
Without Screen							
Trial means	83	58	50	58	58	58	58
Trial σ	41	20	0	20	20	20	20
Error means	17	4	2	4	4	4	4
Error σ	15	3	2	5	2	5	4
With Screen							
Trial means	123	140	93	150	80	97	132
Trial σ	94	65	33	177	60	70	86
Error means	20	30	15	15	10	16	20
Error σ	20	27	11	42	15	21	23

* Means and standard deviations (σ) of trials and errors required to reach a criterion at each delay interval of 90% correct responses in a day's session of approximately 50 trials, without and with an interposed opaque screen.

TABLE 2.—*Visual Delayed-Response Scores* *

Subject No.		Period of Delay, Sec.											
		0		5		10		15		20		25		30	
		T	E	T	E	T	E	T	E	T	E	T	E	T	E
Without Screen															
1	(preop.)	150	38	50	4	50	4	100	13	50	4	100	13	100	12
1	(postop.)	(500)	(191)	...	..	...	..	...	..	...	..	...	..	...	..
2	(postop.)	**50**	**4**	**50**	**4**	**50**	**2**	**100**	**16**	**100**	**8**	(500)	(104)	(100)	(15)
3	(postop.)	(500)	(147)	(100)	(39)	(100)	(36)	(100)	(37)	(100)	(33)	(100)	(28)	(100)	(35)
4	(postop.)	**400**	**105**	(500)	(162)	(100)	(33)	(100)	(38)	(100)	(30)	(100)	(32)	(100)	(47)
5	(preop.)	50	5	50	1	50	0	50	5	50	2	50	4	50	3
5	(postop.)	**250**	**51**	**500**	**108**	(500)	(115)	(100)	(22)	(100)	(36)	(100)	(45)	(100)	(37)
6	(preop.)	100	20	50	2	50	1	50	1	50	5	50	1	50	1
6	(postop.)	**225**	**73**	**100**	**10**	**100**	**13**	**50**	**4**	**50**	**3**	**100**	**16**	**50**	**3**
With Screen															
2	(postop.)	**100**	**10**	**50**	**2**	(100)	(25)	(100)	(36)	(100)	(42)	(100)	(51)	...	..
3	(postop.)	(100)	(38)	(100)	(40)	(100)	(46)	(100)	(46)	...	..	...	..	...	..
4	(postop.)	(100)	(35)	(100)	(37)	(100)	(40)	(100)	(47)	...	..	...	..	...	..
5	(preop.)	50	0	80	7	80	9	80	10	200	39	110	21	140	20
5	(postop.)	(100)	(40)	(100)	(40)	(100)	(41)	(100)	(45)	...	..	...	..	...	..
6	(preop.)	120	39	242	78	150	36	50	3	50	1	50	3	200	65
6	(postop.)	**110**	**9**	**250**	**62**	**193**	**28**	**150**	**20**	**50**	**5**	**50**	**4**	**50**	**2**

* Trials, T, and errors, E, necessary to reach a criterion of 90% correct responses in a day's session of approximately 50 trials, without and with an interposed opaque screen. Scores given in parentheses indicate failure to meet the criterion within the number of trials specified. Postoperative scores are in **boldface**.

TABLE 3.—*Auditory Discrimination Problem* *

Subject No.	Preoperative Training		Preoperative Retention		Postoperative Training	
	Trials	Errors	Trials	Errors	Trials	Errors
1	512	148	...	...	540	127
2	...	...	...	...	1,119	388
3	...	...	...	...	2,375	825
4	...	...	...	...	2,085	704
5	430	110	...	...	330	80
6	597	195	30	1	30	1
N †	438	117	30	9	...	...
Normal group Mean	532	167	...	...	...	...
Normal group σ	114	58	...	...	...	...

* Trials and errors required to reach a criterion of 90% correct responses in a day's session of approximately 30 trials on the discrimination of a bell and buzzer.
† N was a monkey who was trained, and later tested for retention, but never operated on.

three standard deviations from the means of the normal group in both trials and errors. It appears that, except for Animal 6, both initial learning and retention of the discrimination habit were affected by the operations.

Auditory Delayed Response (Table 4).—All subjects, except Animal 6, were considerably handicapped in this problem after operation. Whereas the six normal monkeys were all able to meet the criterion of 90% correct responses at delays of 10 seconds or longer, no animal operated on except Monkey 6 (whose scores were as good after operation as before) achieved this level of performance at delays over 5 seconds. Animals 1, 3, and 4 failed to meet the criterion at 0 second,[14] although the performances of Animals 1 and 4 were significantly above chance at this interval. Animals 2 and 5 failed at 5 and 7½ seconds, respectively. Their scores at these delays, however, differed significantly from chance.

TABLE 4.—*Auditory Delayed-Response Scores* *

Subject No.	Period of Delay, Sec. 0 T	0 E	2½ T	2½ E	5 T	5 E	7½ T	7½ E	10 T	10 E	12½ T	12½ E
1 (preop.)	524	106	30	0	320	57	190	35	150	35	225	46
1 (postop.)	**(3,418)**	**(954)**	...	..	...	..	...	..	...	..	...	..
2 (postop.)	**1,440**	**528**	**90**	**24**	**(2,150)**	**(837)**	...	..	...	..	...	..
3 (postop.)	**(3,170)**	**(1,543)**	...	..	...	..	...	..	...	..	...	..
4 (postop.)	**(3,753)**	**(1,566)**	...	..	...	..	...	..	...	..	...	..
5 (preop.)	620	176	280	68	402	99	192	43	150	36	150	34
5 (postop.)	**1,120**	**339**	**345**	**84**	**225**	**84**	**(2,335)**	**(949)**	...	..	...	..
6 (preop. I)	1,559	570	480	162	60	8	210	43	450	128	120	17
6 (preop. II)	1,262	350	315	76	255	44	1,020	243	120	24	90	11
6 (postop.)	**1,800**	**432**	**90**	**11**	**60**	**9**	**226**	**51**	**120**	**29**	...	..
N † (I)	989	332	90	14	30	2	540	188	106	27	(280)	(111)
N † (II)	1,364	411	660	229	60	5	30	0	60	9	60	7
Normal Group mean	945	311	218	62	270	59	232	62	214	56	...	..
Normal Group σ	373	166	182	64	215	55	187	73	159	48	...	..

* Trials, T, and errors, E, necessary to reach a criterion of 90% correct in a day's session of approximately 30 trials. Scores given in parentheses indicate failure to meet the criterion within the number of trials specified. Postoperative scores are in **boldface.**

† N was a monkey who was trained (I), and later tested for retention (II), but never operated on.

COMMENT

The experiments reported here were undertaken to compare the effects of dorsal, midlateral, and ventrolateral excisions of frontal granular cortex on auditory and visual delayed-reaction problems. More specifically, an attempt was made to provide evidence on three questions: first, the purely psychological one of the independence or dissociation of the symptoms observed; second, the anatomicofunctional question of the relation of defect to the location and mass of tissue removed, and, third, the purely anatomical one of the manner of organization of the projection of nucleus medialis dorsalis on the prefrontal cortex.

Dissociation of Symptoms.—Comparison of the results on the auditory discrimination and auditory delayed-reaction tests shows that if the animals are rated as to

14. The procedure at 0-second delay differed from that used in the auditory discrimination problem in that only in the latter case was the sound still present at the time the animal responded.

ability in each of these problems after operation, the resulting distributions are identical. Thus, of the monkeys trained before operation, Animal 6 was best (relearned in fewest trials); Animal 5, intermediate, and Animal 1, worst, on both problems; of the animals trained only after operation, the order from best to worst was likewise the same for the two problems: Animal 2, then Animal 4, and then Animal 3. The fact that both discriminative learning and delayed reaction were adversely affected in five monkeys, and were both unaffected in the sixth is in disagreement with Jacobsen's [2] conclusion that the defect following prefrontal operation is restricted to delayed reaction. Harlow and Dagnon [15] found prefrontal animals significantly inferior to normal controls in learning visual discriminations. The present study confirms and extends the conclusion of Harlow and Settlage [16] that the particular functions involved in discriminative learning are not independent of the frontal areas.

The similarity of the results on auditory and visual delayed-reaction tests suggests that decrement in postoperative performance is unrelated to the modality through which the differentiating cue is received. Either the disturbance affects some process other than cue reception, or there is a general perceptual abnormality independent of modality. The first of these, illustrated by Jacobsen's conception of "loss of immediate memory," has required modification in view of the findings of various investigators [17] that there is no inability to delay per se. Alterations of the experimental situation, which may be interpreted as perceptually emphasizing the differential cue, result in improved performance. Interpretation of the deficit in delayed-response problems as perceptual in nature (perhaps a reduced scope of responsiveness) is supported by independent evidence of such disorders following frontal-lobe lesions in both man and animals,[18] but more precise specification of the disorder waits upon further experimentation.

Relation of Defect to Location and Mass of Tissue Removed.—As pointed out in the preceding section, the outcomes of the tests of discrimination and delayed reaction were consistent among the experimental group, Animals 6 and 2 showing least postoperative disturbance, Animals 5 and 4 ranking intermediate, and Animals 3 and 1 showing the most disturbance on all tests. Consequently, the several defects may be treated as a unit for purposes of structural-functional correlation.

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Analysis of the lesions indicates that bilateral destruction of the tissue along the sulcus rectus, superiorly and inferiorly, produces the greatest deficit. This condition was fulfilled in all animals except 6 and 2. The lesion in Animal 6 spared the superior bank of the sulcus rectus and the cortex dorsad to the sulcus on the left side. Removal of tissue in Animal 2 was confined to the region above this sulcus. Comparison of the effects of lesion on these two animals suggests that the dorsal region is perhaps of greater importance than the ventrolateral.

The importance of the frontal pole has been emphasized in the literature, but extent of damage to this area cannot account satisfactorily for the results. Degree of damage to the extreme frontal region in Animal 6 was similar to that in Animal 5 and greater than in Animal 2, whose frontal pole was left intact; yet Animals 5 and 2 showed greater behavioral alteration than did Animal 6. The single factor of mass of ablation of prefrontal cortex is also an unacceptable explanation. The predominantly ventrolateral removal in Animal 6, which produced no measurable disturbance on the tests, was at least as large as that in Animal 4, and certainly larger than that in Animal 5, both of whose lesions were midlateral. The lesion in Animal 2 was comparable in extent to that in Animal 5; yet the sequelae were quantitatively dissimilar. It appears probable, however, that mass of tissue removed may explain the differences in severity of symptoms within the midlateral group.

The conception of prefrontal organization which emerges from the present study is that of a unitary region, all or most parts of which are potent, although not equipotent. There appear to be unequal concentrations of function within the region, as indicated by quantitatively different effects of ablations in various regions on level of activity and acquired differential reactions. Removal of the posterior orbital gyrus is reported to be associated with hyperactivity of greater magnitude and rapidity of onset than that following ablation of other frontal areas.[19] The experiments reported here implicate the midlateral part as focal for the production of disabilities in various learning problems, with the dorsolateral part second in importance and the ventrolateral part least concerned. The midlateral and dorsolateral zones may be in part homologous to the "superior midfrontal zone," which Penfield[20] considers to be of prime significance in intellectual defect resulting from frontal-lobe removals in man.

The reasons for the importance of this region remain to be considered. Although the frontal lobe receives an abundant radiation from nucleus medialis dorsalis, it is unlikely that this connection is basic to its role in the delayed-reaction problem, for Jacobsen and Walker[21] have made direct lesions in this nucleus with no resultant loss of ability on the test. It is possible that the participation of this region in circuits involving the parietal and temporal "associative" areas[22] is fundamental.

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22. Bailey, P.; von Bonin, G.; Davis, E. W.; Garol, H. W., and McCulloch, W. S.: Further Observations of Associational Pathways in the Brain of Macaca Mulatta, J. Neuropath. & Exper. Neurol. **3**:413-415, 1944.

These circuits are concerned with interregional, rather than intraregional, influences, and it is reasonable to assume that their interruption might produce widespread cortical dysfunction.

Projection of Nucleus Medialis Dorsalis.—An examination of these cases confirms in general Walker's [23] conclusion that the dorsoventral axis of the prefrontal cortex and that of nucleus medialis dorsalis correspond. It is clear that the anteroposterior axis of nucleus medialis dorsalis does not represent the anteroposterior cortical axis, for lesions confined to the region about the arcuate sulcus give rise to degeneration which spares at least the posterior third of the nucleus (Experiment 9 [23a] and Experiment 5 [12]). In the present study, degeneration of the caudal part of the nucleus was unrelated to the posterior extent of cortical ablation. The second axis of differentiation in the nucleus is probably diagonal, extending from anterolateral to posteromedial, and corresponds to a diagonal axis of the cortex from anteroventral to posterodorsal. A subsequent publication will consider these problems in more detail in connection with a larger series of cases.

SUMMARY

Lesions of the dorsal, midlateral, and ventrolateral parts of the frontal granular cortex and a composite of these ablations were made in a series of monkeys (Macaca mulatta).

The subjects were tested on an auditory discriminative habit and on delayed reaction to auditory and to visual cues.

The animals whose lesions were predominantly in the ventrolateral or dorsal region showed only comparatively slight deficits on the tests; those whose lesions involved the midlateral portion were seriously handicapped on all tests. Among the latter group, total mass of tissue removed appeared to influence severity of symptoms.

Studies of thalamic degeneration were made, and the organization of the projection of nucleus medialis dorsalis is discussed.

23. (*a*) Walker, A. E.: The Primate Thalamus, Chicago, University of Chicago Press, 1938; (*b*) footnote 12.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

THE PERIPHERAL NERVOUS SYSTEM OF LAMPANYCTUS LEUCOPSARUS. D. L. RAY, J. Morphol. **87**:61 (July) 1950.

This thorough investigation of the peripheral nervous system of the lantern fish, Lampanyctus leucopsarus, was undertaken with a twofold purpose: first, to demonstrate the innervation of the photophores in order to shed some light on whether their control is neural or hormonal, and, second, to describe the innervation of all the light organs which are of taxonomic importance in the lantern fishes.

The complete nervous system is described in great detail and illustrated with 40 plates. The innervation of all the photophores is described. The light organs of the body constitute a linear series, most of which, even though they may be elevated, are innervated by the ventral ramus of the spinal nerve of the body segment on which they are located. A description of the sympathetic nervous system is also included.

REID, New Brunswick, N. J.

Physiology and Biochemistry

METRAZOL ACTIVATION OF ACETYLCHOLINE-TREATED CEREBRAL CORTEX. F. M. FORSTER and L. MADOW, Am. J. Physiol. **161**:426, 1950.

Forster and Madow applied acetylcholine locally to the cerebral cortex of experimental animals and then administered metrazol® (pentylenetetrazole U.S.P.) intravenously. Convulsive discharges appeared in the records from the acetylcholine-treated cortex before any spiking discharges were seen in control regions. By careful control of the administration of metrazol,® the convulsive activity could be limited to the area of application of acetylcholine. The authors conclude that the acetylcholine-treated cerebral cortex has a lower convulsive threshold for metrazol® than the nontreated cortex.

FORSTER, Washington, D. C.

EXPERIMENTAL SENSORY-INDUCED SEIZURES. F. M. FORSTER and L. MADOW, Am. J. Physiol. **161**:430, 1950.

Forster and Madow determined the auditory receptive area and somatosensory areas of the cerebral cortex of experimental animals. Acetylcholine was applied to these areas; metrazol® (pentylenetetrazole U.S.P.) was given parenterally, and the stimulus appropriate to the region was administered. Subconvulsive doses of metrazol® coupled with appropriate stimuli after application of acetylcholine to the cerebral cortex resulted in electrical evidence of seizures and clinical convulsions. The seizure discharges began in the area treated with acetylcholine and could be driven to generalization.

FORSTER, Washington, D. C.

ROLE OF THE NERVOUS SYSTEM IN EXPERIMENTAL RENAL HYPERTENSION. W. G. MOSS and G. E. WAKERLIN, Am. J. Physiol. **161**:435, 1950.

Moss and Wakerlin studied the blood pressure levels in normotensive dogs and in dogs with experimental renal hypertension. They concluded that the role of the nervous system was the same in the two groups of dogs. This conclusion was based on the fact that similar changes in the blood pressures occurred in the two groups during surgical anesthesia. Drugs which blocked or reversed the pressor effect of epinephrine acted similarly in the two groups. Drugs which block sympathetic activity elevated the blood pressure in normotensive dogs and in dogs with renal hypertension, but decreased the pressure in dogs with neurogenic hypertension. The studies reveal an increased importance of the nervous system in maintaining the blood pressure level of dogs with neurogenic hypertension.

FORSTER, Washington, D. C.

THE HUMAN PYRAMIDAL TRACT: XVIII. AN ANALYSIS OF ITS PATHOPHYSIOLOGICAL STATUS. A. M. LASSEK, Brain **73**:95, 1950.

Lassek has attempted to correlate pathological findings and the function of the pyramidal tract in man on the basis of what has been reported in the literature during the past 100 years. The results indicate that paralysis of an enduring nature occurred in 57.5% of the cases without evidence of degeneration of the pyramidal tract. The type of pathological lesion and its chronicity are of importance; in the majority of instances, cerebral tumors do not cause secondary degeneration in the motor bundle, although paralytic symptoms may be chronically present; cerebrovascular lesions in general are more destructive to pyramidal neurons; in certain congenital cases in which there are malformations in cerebral development the pyramidal tract may be morphologically intact, although pronounced paralysis may be present.

FRANKEL, Philadelphia.

ON THE RELATION OF POTASSIUM TO THE NEUROLOGICAL MANIFESTATIONS OF HYPOCALCEMIC TETANY. F. L. ENGEL, S. P. MARTIN, and H. TAYLOR, Bull. Johns Hopkins Hosp. **84**:285 (April) 1949.

Engel, Martin, and Taylor state that there are many factors in addition to the level of the serum calcium which are concerned with the actual precipitation of the neurological phenomena of tetany. The purpose of this report is to describe one more factor which enters into the problem of tetany. The authors describe their studies on two patients whose symptoms and signs of hypocalcemic tetany were masked by the simultaneous presence of hypokalemia.

In these patients the ionized calcium of the serum remained relatively constant, fluctuations in signs and symptoms of tetany being correlated with spontaneous increases or decreases in serum potassium. In the presence of hypokalemia and hypocalcemia without tetany, severe tetany could be induced at will by elevation of the serum potassium by intravenous infusion of potassium chloride. Tetany so induced could be abolished by administration of calcium salts without changes in serum potassium, or it disappeared spontaneously when the serum potassium returned to its initial low level after infusion without changes in serum calcium.

The electrocardiographic abnormalities noted were characteristic of hypokalemia and were abolished by the administration of potassium, but not by calcium.

Engel, Martin, and Taylor stress the danger of too vigorous therapy with potassium in the presence of hypocalcemia.

GUTTMAN, Wilkes-Barre, Pa.

PHOSPHATASE OF BRAIN TISSUE. F. BINKLEY and C. K. OLSON, J. Biol. Chem. **186**:725, 1950.

A phosphatase of brain tissue has been obtained in a purified condition. The enzyme was found to hydrolyze inorganic pyrophosphate and to remove the terminal phosphate of adenosinetriphosphate. The activity of the enzyme was dependent on the presence of magnesium ions. Considerable activation of the enzyme was observed when glutathione was added together with the magnesium ions, but maximal activity was obtained only by preincubation of the enzyme with magnesium ions and glutathione. The results were examined in terms of the concept of a protein-metal-substrate complex, as suggested by Bauer and by Jenner and Kay, and certain objections to the concept were noted.

PAGE, Cleveland.

EFFECTS OF pH, BICARBONATE, AND COFACTORS ON THE METABOLISM OF BRAIN SUSPENSIONS. MARION K. BIRMINGHAM and K. A. C. ELLIOTT, J. Biol. Chem. **189**:73, 1951.

Anaerobic glycolysis by brain suspensions shows a pH optimum at about 7.0 in the absence of added pyruvate. In the presence of added pyruvate the rate of glycolysis increases, with the pH rising to about 7.3 and remaining at least 7.9. The slight aerobic acid formation by brain suspensions decreases with decrease in the pH. At pH 6.6 it ceases, and there may be even slight disappearance of acid. Brain suspension contains an active diphosphopyridine nucleotidase, but no evidence could be obtained to indicate that destruction of diphosphopyridine nucleotide seriously limits glycolysis in the dilute suspensions used. It seems that in isotonic suspensions diphosphopyridine nucleotide is held in a form which is not susceptible to destruction by the

enzyme. Bicarbonate buffer, 0.02 M bicarbonate and 5% carbon dioxide, causes about 10% inhibition of the respiration of brain suspensions in a modified Ringer medium. Bicarbonate, 0.04 M and 10% carbon dioxide, causes about 16% inhibition. Phosphate buffer causes an initial stimulation, about 20% with 0.03 M phosphate, which falls off with time. Apparent stimulation of respiration by the addition of small amounts of bicarbonate to a phosphate-buffered medium is due to an artifact. Anaerobic glycolysis by isotonic suspensions occurs at the same rate in bicarbonate-buffered or bicarbonate-phosphate-buffered media as in plain phosphate-buffered medium. However, increasing the carbon dioxide tension from 5 to 10%, while maintaining a constant pH by increasing the bicarbonate concentration, causes a very slight inhibition.

PAGE, Cleveland.

ROLE OF ETHYL ALCOHOL IN THE BIOLOGICAL SYNTHESIS OF CHOLESTEROL. G. L. CURRAN and D. RITTENBERG, J. Biol. Chem. **190**:17, 1951.

The importance of acetic acid as a precursor in the synthesis of cholesterol by the animal body is well established; both carbon atoms participate. Whether acetic acid is utilized in itself or as some other 2-carbon compound remains unknown. Bloch and Rittenberg have shown that ethyl alcohol (CD_3CH_2OH) compares favorably with acetic acid as a precursor in cholesterol synthesis. There is evidence that an aldehyde is an active metabolite in sterol synthesis, and the dismutation of acetaldehyde is known to take place in liver homogenates. This raises the possibility that ethyl alcohol or acetaldehyde may be an intermediate in the utilization of acetate for cholesterol synthesis. Ethyl alcohol is not an immediate precursor in the biological synthesis of cholesterol.

PAGE, Cleveland.

EFFECT OF HYPERINSULINISM ON BRAIN PHOSPHOLIPIDE. E. C. MCGHEE, E. PAPAGEORGE, W. L. BLOOM, and G. T. LEWIS, J. Biol. Chem. **190**:127, 1951.

Massive doses of insulin were administered to 24 rabbits; 12 were given no further treatment, 6 were given 0.5 gm. of lecithin one hour after the insulin, and 6 were given sufficient glucose to maintain the blood sugar above a convulsive level in spite of the insulin dose. Twelve untreated rabbits served as controls. Analyses were made for glucose and lipide phosphorus of whole blood and for lipide phosphorus of whole brain.

Lipide phosphorus of whole blood was not significantly affected by the administration of insulin. However, the insulin treatments produced a consistent and significant decrease in the brain lipide phosphorus of the order of 10%. The decrease was effected in about six hours and was not reversed by the administration of lecithin or glucose.

PAGE, Cleveland.

FURTHER STUDIES OF GLUTAMIC ACID DECARBOXYLASE IN BRAIN. E. ROBERTS and S. FRANKEL, J. Biol. Chem. **190**:505, 1951.

The presence of large amounts of γ-aminobutyric acid and of a very active enzyme for the formation of this substance from glutamic acid suggests that the α-decarboxylation of glutamic acid may be a reaction of major importance in the metabolism of the central nervous system. Similar levels of γ-aminobutyric acid or of decarboxylase activity have not yet been found in any other tissues examined, although there is some evidence that, under certain conditions, small amounts of γ-aminobutyric acid may be formed.

The pH optimum of brain glutamic acid decarboxylase was found to be between 6.4 and 6.5. The Michaelis-Menten constant was estimated to be 6.4×10^{-3} mole per liter. L-Glutamic acid was the only naturally occurring amino acid attacked by the enzyme. D-Glutamic acid and α-ketoglutarate, as well as some of the other substances tested, were found to be inhibitory. Pyridoxal phosphate was highly specific as a coenzyme, pyridoxal, pyridoxine, 4-desoxypyridoxine, 4-methoxymethylpyridoxine, and pyridoxamine being inactive in the system. Experiments with the glutamic acid decarboxylase of brain as a test system showed that synthesis of codecarboxylase probably takes place when pyridoxal and adenosinetriphosphate are added to a homogenate of fresh brain in the presence of fluoride. Only very small amounts of carbon dioxide were liberated anaerobically from glutamic acid by homogenates of muscle, liver, and kidney under the same conditions in which brain homogenate exhibited its maximal activity.

PAGE, Cleveland.

STUDIES ON PAIN: AN INVESTIGATION OF SOME QUANTITATIVE ASPECTS OF THE DOL SCALE OF PAIN INTENSITY. J. D. HARDY, H. G. WOLFF, and H. GOODELL, J. Clin. Invest. **27**:380 (May) 1948.

Using a three-second exposure of the skin to thermal radiation as a painful stimulus, the authors made measurements of the stimulus intensities which evoked painful sensations. Three series of experiments were performed, in the first of which three experienced observers reported the relative intensities of pain in terms of fractions of an 8-dol pain. In the second series of experiments 70 medical students were similarly studied. In a third series of experiments the effects of fatigue and minor mood changes upon discriminations of relative intensity of pain were studied.

The authors determined that the scale of painfulness based on estimations of pain intensity as fractions of a known pain coincides with the scale based on the summing of just noticeable differences in pain sensation. The dol as a unit of painfulness can then be defined as the sum of two "jnd's" (just noticeable differences) in pain sensation, or as approximately one-tenth the intensity of ceiling pain. The accuracy of estimating pain intensity was limited by the ability of the subject to discriminate differences in pain intensity. The limit was ± 0.5 dol; the spread of reports about a mean value was ± 1 dol. Experience in reporting pain intensities, moderate fatigue, and day-to-day variations in mood were not associated with an appreciable change in the ability to estimate pain intensity. The authors conclude that the dol scale provides a satisfactory basis for estimating pain intensity in the following respects: It provides a numerical scale of sensory steps all of which are equal, even though the differences in stimuli corresponding to these steps are not equal. The clinician's interpretations of the patient's estimates of pain in terms of "mild," "moderate," "severe," and "extreme" represent fairly reproducible divisions of the intensity scale of pain. The dol scale is based on a type of stimulus which gives reproducible results in terms of threshold measurements and affords a basis for comparison of other methods of measuring pain intensity, provided these have been made in terms of a reproducible pain.

DONALD, Philadelphia.

THE DISTRIBUTION OF PHOSPHORUS ^{32} IN EARLY CHICK EMBRYOS. ERNEST L. HUNT and JEROME J. WOLKEN, J. Exper. Zool. **109**:109 (Oct.) 1948.

The whites of 302 hen's eggs were injected with P^{32} at 0, 24, and 48 hours of incubation. The embryos were removed about 24 hours after injection and autoradiographs made on No-Screen X-ray Safety Film. Observations on the 72 radiographs used in this study indicated that phosphorus was distributed in certain patterns.

There was usually a striking concentration in rapidly developing and differentiating organs, which appeared at the time that, or very shortly after, these organs started to develop.

An anteroposterior gradient appeared at about the 20-hour stage and remained until the 60-hour stage. A maximum concentration of phosphorus occurred first in the ridges of the primitive streak and was followed by a maximum in the head fold, then in the brain, and, finally, in the optic and auditory vesicles.

A secondary center of phosphorus distribution occurred in the posterior regions of the embryo when tail bud development started. In later stages there was a less pronounced mesiolateral gradient.

These patterns of phosphorus distribution can be correlated with the results of other workers on phosphatase distribution, oxygen uptake, and metabolic activity. They parallel to a large extent the distribution of copper.

REID, New Brunswick, N. J.

SOME OBSERVATIONS ON LOBOTOMIZED PATIENTS BASED UPON ROUTINE NEUROLOGIC EXAMINATIONS. AUGUSTUS S. ROSE, J. Nerv. & Ment. Dis. **109**:201 (March) 1949.

Rose reports the results of neurologic examinations of approximately 100 patients on whom a trephine lobotomy had been performed. At first there is generalized flaccidity with reduced muscle tone, which becomes normal in 6 to 10 days. There is an overreaction to superficial, but not to deep pain, which persists and is noticed clinically in the patient's objections to intravenous

or intramuscular injections and to being shaved with a dull razor. During the first postoperative week all patients have spontaneous reflex emptying of the bladder, which persists from 10 days to a long time. The duration of wetting appears to depend on retraining efforts, return toward mental normality, and many psychologic factors.

There are a short attention span and a poverty of mental activity and of spontaneous movement, during which the patient does not reveal interest or recognition. Regardless of the degree of this lethargic status, the patient may be promptly aroused to momentary alertness and physical activity by application of a pin point to the sole. This state usually changes to a more nearly normal one of interest and reaction to the environment in 2 to 14 days.

The electroencephalographic tracings at first show diffuse irregular, high voltage, slow wave patterns, which return approximately to the preoperative normal.

The spinal fluid pressure may rise to 400 mm. of water, and the total protein to 300 mg. per 100 cc., and the latter may not return to normal for one month. Clinical examinations revealed no evidence of interruption of pathways for volitional movement, coordination of movements, or sensory perception.

The author concludes that lobotomy interrupts nerve pathways involved in the function of control of some basic reflex patterns.

FARMER, Philadelphia.

THE ANTICONVULSIVE ACTION OF HISTAMINE AND OF OTHER VASODILATING DRUGS ON EXPERIMENTAL CONVULSIONS IN MAN. F. KAJTOR, J. Nerv. Ment. & Dis. **112**:511 (Dec.) 1950.

To determine the effect of vasodilating drugs on seizures, patients received intravenous injections of histamine, acetylcholine bromide, carbachol U.S.P., and nicotinic acid prior to injection of convulsive doses of pentylenetetrazole U.S.P. (metrazol®) and induction of seizures by electric stimuli. Effects of inhalation of amyl nitrite and ingestion of glyceryl trinitrate were similarly studied. The anticonvulsant action of histamine against metrazol® was in proportion to the amount of histamine given, but 2 mg. was 100% effective in inhibiting seizures. This was evident for 25 to 40 seconds after the injection of histamine, when the fall of blood pressure was greatest. Acetylcholine inhibited seizures, but to a less degree than histamine and more than amyl nitrite. Carbachol U.S.P. only prolonged the preconvulsive period of the seizures. Epinephrine and ergotamine tartrate given with histamine did not alter the anticonvulsant action of the latter. Glyceryl trinitrate and nicotinic acid were ineffective in preventing seizures. Histamine did not prevent electrically induced seizures. The author states that since intense cerebral vasodilatation did not correlate directly with the seizures, the effect produced in inhibiting seizures is related to action on the nerve cells.

BERLIN, Chicago.

AN OBSERVATION ON THE EFFECT OF STRYCHNINE ON LOCAL CORTICAL POTENTIALS. C. HSIANG-TUNG, J. Neurophysiol. **14**:23 (Jan.) 1951.

Strychnine, a powerful convulsant, has been widely used in experimental physiology as a useful instrument in the analysis of electrical activities in the central nervous system. In spite of its wide application in clinical and experimental studies, the mechanism underlying the convulsive action of this drug remains obscure.

In the course of a study on the potential changes in the isocortex in response to a single electric shock applied to the cortical surface, it was found that the local cortical potential could be modified in a characteristic manner by superficial application of strychnine to the cortex.

The pattern of the local cortical potential could be modified by superficial application of strychnine to the cerebral cortex, so that both the size and the promptness of onset of the second component were enhanced without significantly affecting the first component. When the action of strychnine was fully developed, the two components became fused into a single wave, which, however, could be dissociated again into two temporally separated waves by reducing the stimulus strength. It is suggested that the effect of strychnine is probably to accelerate the process of impulse initiation of individual neurons in the central nervous system, so as to increase the efficiency of summation and to increase the chance of synchronization.

ALPERS, Philadelphia.

FUNCTION OF MEDULLATED SMALL-NERVE FIBERS IN MAMMALIAN VENTRAL ROOTS: EFFERENT MUSCLE SPINDLE INNERVATION. S. W. KUFFLER, C. C. HUNT and J. P. QUILLIAM, J. Neurophysiol. **14**:29 (Jan.) 1951.

Medullated fibers of varying diameters pass from the ventral roots to vertebrate skeletal muscle. In mammals such as the cat, about one-third of this innervation to muscle may consist of nerve fibers of small diameter (3 to 8 μ). This paper is concerned with the function of such fibers in the cat. The lumbosacral ventral-root outflow in the cat contains about 30% myelinated nerve fibers of 3 to 8 μ diameter. The function of these fibers was investigated in several muscles, in particular the soleus and tenuissimus.

Nerve fibers of varying diameters were isolated and stimulated in the ventral roots. It was found that fibers of small diameter, conducting at 15 to 55 meters per second, did not cause a detectable muscle contraction or set up propagated muscle impulses in ordinary muscle fibers. Fibers conducting at a faster rate always caused the well-known motor unit twitch response accompanied with propagated muscle impulses.

Small-nerve stimulation caused small potential changes, which could be detected in thin tenuissimus muscles. It is concluded that these potentials originate in the intrafusal muscle fibers of spindles. Small nerve fibers tend to divide and innervate several muscle spindles.

Small-nerve stimulation increases the existing afferent discharge rate of stretch receptors or causes discharge in receptors which are "quiescent." One can best detect these effects by recording discharges in the dorsal roots from single spindle afferent fibers while stimulating single efferent small nerve fibers.

The effectiveness of small-nerve stimulation is greatly modified by various degrees of muscle stretch, being increased by high muscle tensions and decreased by lower tensions. The effect of variations in tension on the receptor discharge can be compensated for over a wide range by altering the number and/or frequency of small-nerve stimuli.

The excitatory effect of small-nerve stimulation on the spindle discharge shows a phenomenon of facilitation; the number of afferent discharges increases progressively during continued stimulation until a steady discharge rate is established. At a given muscle tension, the facilitation period is shorter with higher frequencies of stimulation, and the maximal spindle discharge rate is also higher.

The discharge rates of some spindle receptors, after a period of facilitation, can become identical with the frequency of small-nerve stimulation. This "driving" effect, like all spindle discharge patterns, is influenced by muscle tension; it can be duplicated by applying mechanical oscillations to the tendon or muscle.

Small-nerve stimulation is followed by fluctuations in excitability, as indicated by the spindle discharge. It is thought that the period of depression originates mainly in the sensory nerve terminals.

All the evidence indicates that small-nerve excitation acts by causing contractile changes in the intrafusal muscle fibers, which then excite the sensory endings by stretch-deformation effects.

The possible role of small-nerve activity in reflex function is briefly discussed. This efferent system appears well suited to act as a peripheral regulator of the proprioceptive spindle mechanism.

ALPERS, Philadelphia.

THE MECHANISM OF SKULL FRACTURE. E. S. GURDJIAN, JOHN E. WEBSTER, and H. R. LESSNER, J. Neurosurg. **2**:106 (March) 1950.

The authors used "stress-coat" studies to delineate deformation patterns of the skull following impact. It was found that the production of a depressed or linear fracture depended mainly on the velocity and energy of the injuring object and, to a less extent, on its shape and size.

The "stress-coat" method utilizes a strain-sensitive lacquer that will crack under tension stresses. The inner and outer tables of the skull were coated with lacquer; cracks appearing on the outer surface result from outbending of the skull, and those appearing on the inner table, from inbending. In this manner, accurate deformation patterns were obtained. It was shown that after impact there was always an area of inbending at the point of the blow. With an adequate amount of velocity and energy the area of inbending may fail, resulting in a depressed

fracture at the site of the blow. If the energy is not sufficient to cause a depressed fracture, the skull rebounds. Peripheral to these areas of inbending are discrete areas of outbending; this outbending may be severe enough to produce tearing-apart forces, resulting in a linear fracture. The fracture then extends both toward the point of impact and away from it, along lines of greatest tensile stress in areas where outbending occurred. The authors have conclusively proved that tearing-apart forces due to an impact are produced by bending of the bone, and not by direct stress.

TOZER, Topeka, Kan.

Diseases of the Spinal Cord

EPIDEMIC POLIOMYELITIS: REVIEW OF 526 CASES. M. LENARSKY, R. L. PARR, and H. E. SEANOR, A. M. A. Am. J. Dis. Child. **82**:160 (Aug.) 1951.

Lenarsky and his colleagues discuss the significant clinical and pathologic findings in 526 cases of poliomyelitis occurring in the latter half of 1949 in New York. There were 141 (26.8%) nonparalytic and 385 (73.2%) paralytic cases. Bulbar involvement occurred in 126 cases (23.9%).

There were 40 deaths; 39 were of patients with bulbar involvement. Complete vascular collapse resulting from failure of the vasomotor center accounted for 33 deaths (82.5%). The availability of the respirator for respiratory difficulty due to peripheral or central failure and the use of central stimulation for the latter minimized fatality from these causes.

Vomiting of coffee-ground material, considered an unfavorable prognostic sign, occurred in 16 patients with bulbar poliomyelitis, 11 of whom died. The pathologic features demonstrated in the stomachs at autopsy were edema and intense congestion of the capillary bed, perivascular extravasation of blood, and focal erosion of gastric mucosa, with evidence of blood in the gastric cavity. Congestion of Peyer's patches of the ileum was frequently found. The authors discuss the various hypotheses suggested as causes of the gastrointestinal lesions in poliomyelitis.

Muscular pain was not a predominating feature in this series. Drugs for the relief of pain and muscular tightness did not prove effective. The response to hot packs was satisfactory.

The possibility that lesions of poliomyelitis may be on the basis of an allergic reaction led to the treatment of a group of 10 patients with prophenpyridamine ("trimeton") maleate. No therapeutic value seemed to result. Aureomycin in large doses was given to 38 control patients with nonparalytic poliomyelitis, without effect on the clinical course of the disease. An automatic refrigerating unit was used in 18 cases, and the impression gained was that the apparatus produced an antipyretic effect but did not alter the course of the disease.

The patients with bulbar involvement were treated by postural drainage, pharyngeal suction, parenteral feeding, oxygen by nasal catheter, and prevention of pulmonic emboli by changes of position and use of antibiotics. Tracheotomy was performed on six patients when other treatment failed to maintain an adequate airway, but all six died.

There were 26 patients with encephalitic involvement. These patients showed varying degrees of disorientation, confusion, drowsiness, and coma.

Involvement of the vital centers in poliomyelitis are serious and are responsible for almost all the deaths from this disease. In this series two drugs were used as central stimulants, with success in some instances. Caffeine and sodium benzoate U. S. P. was used for central respiratory depression, and phenylephrine (neo-synephrine®) hydrochloride, 1%, for failure of the vasomotor center.

The respirator had its prime use in the respiratory difficulty due to involvement of the muscles of respiration, the intercostal muscles, and the diaphragm, and treatment was most successful in such cases. Patients were placed in the respirator before exhaustion ensued. To avoid overdependence on the respirator, weaning was started early, even the first day when possible.

The respirator is not so effective when there is bulbar involvement, although with severe central respiratory depression it can be of help.

Transportation of the acutely ill poliomyelitis patient over long distances ("transportation fatigue") may contribute to the severity of involvement and to the mortality rate. In this series of cases 15 of the 40 deaths occurred within 24 hours after hospital admission; 9 of the patients were transported from considerable distances.

ALPERS, Philadelphia.

A Syndrome in Acute Cervical Spine Injuries for Which Early Operation Is Indicated. R. C. Schneider, J. Neurosurg. **8**:360 (July) 1951.

Schneider reports two cases of acute cervical-spine injury with a syndrome consisting of immediate complete paralysis with hypesthesia at the level of the lesion, but with preservation of touch sense and the retention of vibration sense. A ruptured nucleus pulposus was diagnosed preoperatively in both cases and found at operation, although this was in conjunction with a compression fracture of the cervical body in the second case.

The mechanical-stress concept, first described by Kahn in his presentation of the role of the dentate ligaments in chronic compression of the anterior portion of the cord, is the basis on which it is believed the symptoms in these two cases may be explained.

The first patient was not operated on until the 11th day after injury. It is the author's belief that if this patient had been operated on sooner, his convalescence and recovery would perhaps have been more rapid and complete. Because of this experience with the first patient, the second was operated on as an emergency. The latter had a more rapid recovery.

While the treatment of cervical-spine injuries with involvement of the cord is controversial, Schneider believes that an injury to the cervical portion of the cord ought to be regarded as an acute surgical emergency. The patient should be examined early, and if proper indications are present he should be operated on immediately. The cord does not tolerate acute compression for any length of time, because edema, anoxia, and irreversible changes soon occur. The author reviews indications for early operation in cases of cervical-cord injuries, and the acute dentate-ligament syndrome, here described, is included as an additional criterion for early operative intervention.

Alpers, Philadelphia.

Compression of Spinal Cord by Aneurysm of Descending Thoracic Aorta. C. de Luccia, J. Zaclis, and R. Araujo, Arq. neuro-psiquiat. **9**:85 (March) 1951.

A white man aged 54 was admitted to the hospital complaining of numbness and weakness of the lower extremities of about four months' duration; there was also some difficulty with urination. He had a history of syphilis 20 years previously and of treatment for aortitis. There were no complaints referable to the cardiovascular system on his admission. Neurological examination showed spastic paresis with a bilateral Babinski sign and a sensory level at the eighth thoracic segment. Serological reactions of the blood and spinal fluid were negative. There were 6 cells per cubic millimeter of spinal fluid, of which 76% were lymphocytes; a total protein content of 18 mg. per 100 cc., and a positive Pandy reaction. Manometric examination showed partial block, with stoppage of iodized oil between the third and fourth thoracic level. X-ray examination showed an aneurysm of the thoracic aorta, with partial calcification. Erosion of the dorsal vertebrae was evident.

Savitsky, New York.

Poliomyelitis After Tonsillectomy and Trauma. V. Gaustad, Nord. med. **38**:877 (April 30) 1948.

Gaustad reports two typical cases of poliomyelitis after tonsillectomy, with onset 9 and 19 days, respectively, after the intervention. The first case was marked at the start by encephalitic symptoms, followed by spinal symptoms; the early signs of transient changes in character are ascribed to the encephalitic component in the process. In the second fatal case in which only the right tonsil was removed, bulbar symptoms predominated. There was facial paralysis on the right side, suggesting the possibility of a causal relationship between the tonsillectomy and the ipsilateral paralysis. Mention is made of three additional cases of poliomyelitis following tonsillectomy, in one case with one day, in two cases with 42 and 60 days, respectively, between the operation and the outbreak of the disease. In a case in which poliomyelitis set in seven weeks after appendectomy, muscles situated near the site of the operation were paralyzed, especially the right psoas muscle. A lesion to the left of the chin due to trauma may have been the portal of entry for the poliomyelitis virus in the last case, in which the localization of the trauma agreed with the later massive facial paralysis.

J. A. M. A.

ARACHNITIS (CHRONIC LEPTOMENINGITIS): REVIEW. M. FOG and P. THYGESEN, Ugesk. læger **112**:243, 1950.

Fog and Thygesen define arachnitis as an inflammatory-like process of varying extent and intensity, which can occur after different noxae—chemical, mechanical, traumatic, and possibly infectious—or from unknown cause. The primary and dominating tissue changes are in the soft membranes of the brain but may also be present in the nerve roots, cerebrum, and spinal cord. Clinically, intracranial and intraspinal arachnitis should be differentiated; in rare cases they may be combined. Both are oftenest diffuse. In general, the older the process and the greater the extent to which it has involved the parenchyma, the graver the prognosis, but subjective recovery occurs spontaneously in many mild cases. The outlook is favorable in cases in which adhesions and solitary cysts are successfully removed by operation, especially in cases of short duration. Arachnitis is primarily diagnosed by the close relation of the leptomeninges to the nerve roots and the parenchyma of the central nervous system. The unaffected general condition, particularly the fluctuations of cryptogenic aggravations alternating with unexplained remissions in an otherwise chronic course, are characteristic. Polyradiculitis, (radiculo) meningoencephalitis, myelitis, and encephalitis are to be considered in the differential diagnosis. J. A. M. A.

Peripheral and Cranial Nerves

TONSILLECTOMY IN EXPERIMENTAL POLIOMYELITIS. H. VON MAGNUS and J. L. MELNICK, Am. J. Hyg. **48**:113 (July) 1948.

Von Magnus and Melnick demonstrated that after tonsillectomy Cynomolgus monkeys are more susceptible to infection after being fed poliomyelitis virus than rhesus monkeys and African green monkeys. The incidence of poliomyelitis in tonsillectomized Cynomolgus monkeys increased to 93% (13 infected of 14 fed the virus) from a control level of 13 % (2 of 15) for the nontonsillectomized Cynomolgus group. The incidence of 8% in the other tonsillectomized species was no different from the incidence of 8% in nontonsillectomized controls of these species. Two of three Cynomolgus monkeys which contracted poliomyelitis were found to excrete virus with their stools the day before paralysis. Five nonparalyzed monkeys did not excrete virus in the four-week observation period. Of 14 tonsillectomized monkeys which subsequently had poliomyelitis, only 2 had the bulbar form of the disease. Two other monkeys exhibited facial paralysis, together with paralysis of the limbs. J. A. M. A.

POLYNEURITIS: COMPLETE PHARYNGEAL AND RESPIRATORY PARALYSIS WITH RECOVERY. L. R. WEBB JR., Arch. Int. Med. **86**:574 (Oct.) 1950.

Among the neurologic disorders classified as "polyneuritis" are those falling into a rather large group which is most commonly referred to as the Guillain-Barré syndrome. As a group they are distinguished by their involvement of the peripheral nerves and their excellent prognosis. While recovery is one of the distinguishing features of the disease, numerous fatalities have been reported. In a survey of 25 deaths reported in the literature, 23 were due to involvement of the muscles of respiration. Despite the serious implications of respiratory paralysis, the degree to which it may occur and yet be followed by recovery is astonishing. The case here reported is an example.

The patient, a man aged 50, had had a mild sore throat one week before hospitalization. Polyneuritis developed, with respiratory paralysis of two weeks' duration and pharyngeal paralysis of six days' duration, followed by recovery. Webb points out that the early use of the mechanical respirator, tracheotomy, and heavy sedation during the acute phase were valuable aids in management. ALPERS, Philadelphia.

SITE OF LESION IN PARALYSIS OF TWELFTH AND/OR SEVENTH CRANIAL NERVE. K. TSCHIASSNY, Arch. Otolaryng. **51**:739 (May) 1950.

Interesting observations in a case of bilateral complete paralysis of the tongue (panglossoplegia) were the occasion for these studies. A white woman aged 57 was referred to the hospital because of inability to chew, to swallow, or, particularly, to talk in an understandable manner.

The diagnosis offered by the neurological service was progressive bulbar paralysis, probably related to amyotrophic lateral sclerosis. The condition of the facial musculature was regarded as indicative of slight weakness of the facial nerve of the upper motor neuron type.

In this case of complete panglossoplegia, paralysis of the orbicularis muscle and persistence of some voluntary forward movement of the tongue presented two problems. The former is explained, according to Bing, by the fact that the nerve fibers responsible for the motor supply of this muscle originate mainly in the nucleus of the 12th nerve. On the basis of this anatomic peculiarity, paralysis of the orbicularis oris muscle associated with paralysis of the 12th nerve represents a sign indicative of nuclear location of the lesion of the hypoglossal nerve. It is assumed, on the same basis, that in cases of facial paralysis the selectively preserved action of this muscle can be of topognostic value in differentiating nuclear and supranuclear lesions, on the one hand, and infranuclear lesions, on the other. In peripheral lesions of the facial nerve it may be particularly useful in topognosis of the nuclear versus the infracordal locations of the lesion.

The second problem is presented by the presence of some restricted forward movements of the tongue. These movements are explained and proved to be caused passively by the action of the geniohyoid muscles, which are not supplied by the 12th cranial nerve. For this purpose, a special roentgenologic technique, the "superimposed double exposure," was adapted. The movement of the hyoid bone caused by the attempt to move the tongue was demonstrated objectively. These movements of the tongue can therefore be regarded as passive. Their presence does not contradict the diagnosis of complete paralysis of the 12th nerve, but their absence may well be of topognostic value in differentiating extracranial lesions from intracranial lesions in the instance of panglossoplegia.

ALPERS, Philadelphia.

NEUROFIBROSARCOMA OF THE FACIAL NERVE INVOLVING THE TYMPANO-MASTOID. M. R. GUTTMAN and M. A. SIMON, A. M. A. Arch. Otolaryng. **54**:162 (Aug.) 1951.

Neurinoma and neurofibrosarcoma, the one a benign and the other a malignant growth, of the intratemporal portion of the facial nerve constitute a rare and infrequent cause of facial paralysis. They present a clinical picture that is clear and easily distinguished from that of other types of facial paralysis of the peripheral type, since they are not attended by pain, headache, or disturbances of equilibrium. They produce deafness, granulations in the canal, and otorrhea late in the course of the disease. The deafness is of the conductive type. Prognosis is good for life expectancy and poor for recovery from the facial paralysis.

Guttmann and Simon report a case of neurofibrosarcoma in which the patient came to operation at the age of 43, symptoms having been present for almost 10 years. In addition to the case reported, there was microscopic evidence of malignancy in only one case in a total of 18 cases recorded in the literature. In spite of the difference in the histologic picture, the clinical course in these two cases showed only insignificant variation from that of the other 16 cases.

ALPERS, Philadelphia.

MULTIPLE NEURITIS AND HYPOTHYROIDISM. FRED P. CURRIER and J. RUSSELL BRINK, Dis. Nerv. System **9**:144 (May) 1948.

Currier and Brink report two cases of peripheral neuropathy, in both of which the neuritis was closely associated with metabolic changes. The first patient was a woman, aged 40, whose illness resembled pernicious anemia with typical neurologic symptoms. However, free hydrochloric acid was found in her gastric contents, and there was no response to treatment with liver and vitamin B complex. The basal metabolic rate was —27%, but the blood cholesterol was only 80 mg. per 100 cc. It is not known whether this chemical paradox had any relation to the development of the neuropathy. The second patient was also a woman, age not stated, who presented a problem of acute multiple motor neuritis, hypervitaminosis A, low glucose tolerance, and a basal metabolic rate of —8% after being on thyroid medication for a year. Her blood cholesterol was 150 mg. per 100 cc. It is of interest to speculate whether there was any antagonistic relation between the carotinemia and the thyroid metabolism, causing a secondary neuropathy, or whether disordered liver metabolism may have played a causative role. Both patients have improved, subjectively and objectively, on prolonged thyroid medication.

BEATON, Tucson, Ariz.

INFECTIVITY OF NEURAL LEPROSY. A. R. DAVISON, Internat. J. Leprosy **17**:247 (July-Sept.) 1949.

Davison says that most countries in which leprosy legislation has been found necessary have divided their control measures into two sections: that concerned with open, or bacillus-discharging, patients, and that concerned with closed, or bacillus-negative, patients. All cases of lepromatous leprosy fall in the first group, and most cases of neural leprosy in the second. Although it has been demonstrated that neural leprosy is much less infective than lepromatous leprosy, the author warns that this should not be interpreted that neural leprosy offers no public health problem. He refutes this argument on the following grounds: 1. Neural leprosy is caused by Mycobacterium leprae in the skin, as well as in the nerves. 2. Patients with neural leprosy sometimes discharge Myco. leprae. 3. Patients with neural leprosy have infected others. 4. Endemic leprosy can become epidemic. He cites corroborating evidence for these points and analyzes data on 157 patients with neural leprosy admitted in 1940 to the Westfort Institution, in Pretoria, Union of South Africa. Since no less than 38 of these 157 patients with neural leprosy have shown bacillus-positive smears, it appears that a great many more would have become dangerous to the public health if they had not been segregated and treated. Twenty-two of these 38 patients with neural infections had become lepromatous. To prove that endemic leprosy can assume epidemic proportions, the author cites the case of the island of Nauru. In 1920 there were three known cases in a population of about 2,600; in that year there was an influenza epidemic; four years later 30% of the population showed signs of leprosy. J. A. M. A.

PARALYSIS CAUSED BY PENICILLIN INJECTION: MECHANISM OF COMPLICATION—A WARNING. J. M. TARLOV, J. PERLMUTTER and A. J. BERMAN, J. Neuropath. & Exper. Neurol. **10**:158 (April) 1951.

While peripheral neuritis as a complication of the intramuscular injection of penicillin appears to be uncommon, cases of its occurrence have been reported. The present work is an experimental attempt to elucidate the probable mechanism responsible for this complication. In the experiments the rabbit sciatic nerve was used. Tarlov and his co-workers found that the neuritis is attributable to the introduction of the material directly into the parenchyma of the nerve. The resultant inflammatory reactions are much more intense with oily than with soluble solutions of penicillin. Streptomycin injections produced similar reactions. The intense and persistent neuritis, accompanied with severe interruption of nerve function, does not result from the injection of penicillin around the nerve or into its epineurial sheath, or from hemorrhage into or around the sciatic nerve. The nerve sheaths appear strongly to resist the inflammatory reactions and thus to protect the nerve fibers.

After the injection of penicillin into a nerve, a latent interval, varying from 8 to 17 days, sometimes elapsed before severe impairment of nerve function (loss of spread reflex in the rabbit) occurred. This delayed impairment is the experimental counterpart of the similarly delayed onset of symptoms referable to neuritis in human cases, in which neuritis was probably due to progressive inflammatory and fibrotic changes.

The authors point out that when one is administering penicillin or any other form of intramuscular therapy, it is imperative to make one's injections remote from the site of any of the large nerve trunks. The chosen site for intragluteal injections should be the upper outer quadrant. In view of the danger of pulmonary embolism, it is important also to guard against the intravenous injection of the oily suspension of penicillin. Repeated aspiration of the material should be attempted during the injection. ALPERS, Philadelphia.

ADVANCE OF FUNCTIONAL RECOVERY AFTER RADIAL NERVE LESIONS IN MAN. R. E. M. BOWDEN and D. A. SHOLL, Brain **73**:251 (June) 1950.

Bowden and Sholl studied 31 patients in whom there was injury of the radial nerve; all the patients showed signs of recovery in all the muscles normally supplied by the nerve. Using Sunderland's anatomical data, the distances between the suture or lesion and the muscles supplied by the radial nerve were calculated and plotted against the respective times taken for recovery. The process of advance of appearance of recovery of function could be fitted by a curve represented by the formula $y = a + b \log t$; hence, the rate of advance of recovery from muscle to

muscle is at first high and then declines. The advance of appearance of voluntary activity was most rapid in those cases of lesions in continuity in which a complete motor recovery was ultimately made. The level of the lesion affects the distance that recovers in a given time, its effects increasing with the time after suture or injury.

FRANKEL, Philadelphia.

CERVICAL SYMPATHETIC PARALYSIS. J. DONALDSON CRAIG and R. C. FULLER, Brit. M. J. **1**:1182 (June 19) 1948.

Craig and Fuller call attention to the fact that the description of the effects of unilateral paralysis of the cervical sympathetic chain (Horner's syndrome) usually given in standard textbooks is not only inaccurate and incomplete but differs from that published in 1869 by Horner himself. The syndrome is usually considered to consist of ptosis, enophthalmos, pupillary constriction, and anhidrosis of the face on the affected side. Craig and Fuller state that the true clinical syndrome is fairly constant regardless of the site of the lesion. Myosis occurs constantly and is greater in lesions involving the superior cervical ganglion than in those arising more centrally. The apparent enophthalmos is an optical illusion arising from narrowing of the palpebral fissure; it has been shown that sympathetic paralysis produces no immediate enophthalmos and in long-standing cases there is only a slight degree of recession. Hypotonia, depigmentation of the iris, and cataract may occur. Anhidrosis is confined to one side of the face. Vascular changes depend upon the extent of the paralysis, the rapidity of onset, and the presence of other vascular lesions. Some degree of facial hemiatrophy may occur in establishing cases.

ECHOLS, New Orleans.

SIXTH-NERVE PALSY AFTER LUMBAR PUNCTURE AND SPINAL ANALGESIA. R. BRYCE-SMITH and R. R. MACINTOSH, Brit. M. J. **1**:275 (Feb. 10) 1951.

Bryce-Smith and MacIntosh report two cases of paralysis of the sixth nerve, following lumbar puncture in one and spinal analgesia in the other. In both cases a large-bore needle was used which caused rapid loss of considerable cerebrospinal fluid. Paralysis of the external rectus developed in the eye opposite the side on which the patient was lying.

The authors are of the opinion that paralysis of the sixth nerve following spinal analgesia probably occurs oftener than the highest incidence reported (1%) would indicate. The paralysis does not appear until 3 to 21 days after the spinal analgesia and is usually preceded by complaints of severe headache, and perhaps dizziness, nausea, stiff neck, photophobia, and diplopia. Three theories as to the cause of the paralysis are considered: (1) mechanical, (2) toxic, and (3) inflammatory.

ECHOLS, New Orleans.

PARALYSES FOLLOWING IMMUNISING INJECTIONS. GUY BOUSFIELD, Lancet **1**:1028-1032 (May 12) 1951.

Bousfield reports that poliomyelitis seems to occur much less often in the first months of life than in the next few years of childhood. As the risk of postinjection poliomyelitis is probably proportional to the liability to contraction of the disease, he suggests that immunization against diphtheria should be undertaken at about the age of 2 to 5 months. He shows that infants can be immunized successfully at this age and that in the great majority the immunity holds good some 18 months to 2 years later. Active immunity was obtained in 98.9% of Schick-positive infants by the sixth or seventh month of life. He found that the diphtheria prophylactics are best given subcutaneously, and he believes the intramuscular route should be avoided.

ECHOLS, New Orleans.

GLOSSOPHARYNGEAL NEURALGIA AND TUBERCULOUS LARYNGITIS: RECOVERY WITH STREPTOMYCIN. J. C. REY and E. CANEPA, Prensa méd. argent. **38**:1694 (July) 1951.

A man aged 55 with pulmonary tuberculosis had onset of attacks of what was considered idiopathic glossopharyngeal neuralgia. The attacks were severe, coming on five or six times a day. Between them he had a sensation of dryness in the mouth.

At first an otolaryngologic examination revealed no cause for the syndrome, and a diagnosis of glossopharyngeal neuralgia was made. A lumbar puncture showed no abnormality, and the

amount of total protein was normal; there was only 1 cell per cubic millimeter of cerebrospinal fluid. The results of bacteriologic and serologic studies were normal. Another laryngoscopic examination revealed tuberculous laryngitis. The glossopharyngeal neuralgia cleared up completely after a course of streptomycin therapy. The authors know of no other case, in their own experience or in the literature, in which there was such a close relation between glossopharyngeal neuralgia and tuberculous laryngitis.

N. Savitsky, New York.

Polyneuritis Following Cutaneous Diphtheria and Other Skin Infections. H. Strotzka, Wien. klin. Wchnschr. **61**:394 (June 24) 1949.

Strotzka reports on nine cases of severe polyneuritis, in several of which the condition followed proved cutaneous diphtheria; in others the disease was strongly suspected, while in the rest the neuritis was due to other suppurative lesions of the skin. From a review of the cases, it is concluded that paralysis of accommodation is characteristic of diphtheritic polyneuritis, while paralysis of the palate occurs usually if there was a pharyngeal localization of the infection.

Mason, New York.

Vegetative and Endocrine Systems

Postpartum Necrosis of the Anterior Lobe of the Pituitary Gland: Sheehan's Disease. J. E. Cook, W. Bean, M. Franklin, and J. F. Embick, A. M. A. Arch. Int. Med. **87**:517 (April) 1951.

The purpose of this paper is to describe the clinical and pathologic features of postpartum necrosis of the pituitary gland and to point out pitfalls in the diagnosis and therapy, based on seven cases observed during a 15-year period. The diagnosis in four cases was verified by autopsy. Three patients are still alive, and the diagnosis of their condition is based on typical clinical and laboratory findings.

Sheehan estimated that in each 10,000 of the population there are approximately 2 cases of severe postpartum pituitary necrosis and 7 of less severity. He explains the pathogenesis as follows: Normally, after delivery there is a rapid involution of the pituitary gland from its physiologically hypertrophied state during pregnancy. The blood supply of the gland is thus suddenly reduced; if this is complicated by circulatory collapse due to hemorrhage, the blood flow may be reduced to an extremely low level. Thrombosis may thereby be precipitated in the sinuses of the gland, with consequent infarction and necrosis. In six of the seven cases here reported the last delivery had been complicated by severe hemorrhage.

The typical early lesion in the anterior lobe of the pituitary is coagulative necrosis or ischemic infarct, apparently secondary to fibrin thrombi in the sinuses of the gland. The middle and posterior pituitary lobes are rarely infarcted. In the late lesions of Sheehan's disease in the fully developed case which has originated from the early necrosis, the entire pituitary gland appears shrunken, although microscopically only the anterior lobe is involved. The normal structure is replaced by connective tissue with few cells. The thyroid, adrenal, and sex glands are usually atrophied, while the other organs are all smaller than normal, although unchanged histologically. The brain, although usually normal in size may show degenerative changes in the cortex and other areas, perhaps secondary to the pituitary lesion.

To make a diagnosis, the history of a collapse resulting from severe hemorrhage following the last delivery is most helpful. Usually symptoms emerge imperceptibly out of the debility following delivery. Amenorrhea usually persists from the time of delivery; genital and breast atrophy and loss of axillary and pubic hair usually occur. Asthenia, somnolence, mental and psychic changes, and intolerance of cold are common. The weight may not be seriously disturbed. A waxy pallor of the skin is common. The general appearance of a patient with Sheehan's disease may resemble that of a myxedematous person.

Some patients die of intercurrent infections, but most die in coma. One variety of coma is predominantly hypoglycemic, and parenteral administration of dextrose solution will relieve it. The second type resembles an Addisonian crisis and is associated with dehydration, shock, loss

of sodium chloride and fluid, hyperpotassemia, and hypoglycemia. The four deaths in this series were of the second type. In two of the nonfatal cases there were several severe attacks of coma, which were predominantly hypoglycemic with milder aspects of Addisonian crisis.

The best form of therapy for the disease is prophylactic, with better obstetric care and recognition and correction of the complications of pregnancy which predispose to collapse during and after delivery. In the early stages of Sheehan's disease the ideal form of therapy would be hormone replacement with extracts of the anterior lobe. In the past, substitution therapy with available pituitary extracts has been unsatisfactory. Use of corticotropin as early replacement therapy for adrenocortical insufficiency in Sheehan's disease offers hope. Therapy must be aimed at correcting secondary glandular deficiencies. The use of antibiotics is indicated for intercurrent infections, which often induce hypoglycemic coma and adrenal crisis. It should be realized that the treatment of a patient with Sheehan's disease is not simple and often proves unavailing, despite all efforts of the physician.

ALPERS, Philadelphia.

Treatment, Neurosurgery

TRANSORBITAL LOBOTOMY IN THE RELIEF OF INTRACTABLE PAIN. J. M. WILLIAMS and WALTER FREEMAN, A. M. A. Arch. Surg. **63**:203 (Aug.) 1951.

Williams and Freeman treated 23 patients with intractable pain by bilateral transorbital lobotomy. Most of the patients had far-advanced malignant neoplasms and had become addicted to the use of narcotics. The operation was immediately effective in all cases; but there were two postoperative deaths, and in five cases the pain recurred after two weeks. The number of failures probably would have been greater had the patients survived longer. The addiction to narcotics was overcome, or at least considerably improved, in most instances.

Transorbital lobotomy has a definite place in the relief of suffering, since the operation may be performed with the use of local anesthesia, without too much risk, even in the case of enfeebled patients.

LIST, Grand Rapids, Mich.

STELLATE GANGLION BLOCK IN CEREBROVASCULAR ACCIDENTS. W. A. NOSIK, Ann. Int. Med. **35**:409 (Aug.) 1951.

Though it has been accepted for years that the vasomotor control of the cerebral vessels is either very weak or nonexistent and that such alterations as do occur are secondary to cardiac output and vasomotor reactions elsewhere in the body, more recent work indicates that the cerebral vessels are responsive to sympathetic and parasympathetic stimulation, just are as other vessels elsewhere in the body.

The following factors regulate the blood flow in the brain:

1. Extracerebral factors, i. e., systemic arterial pressure.

2. Cerebral factors. Active changes in caliber of cerebral arteries are due to changes in tone of the arterial wall and serve to compensate for fluctuations in the systemic arterial pressure. These changes may be instituted by (*a*) direct trauma, to the vessel wall; (*b*) chemical changes in arterial blood (carbon dioxide, alcohol, etc.); (*c*) asphyxia of tissue due to slow blood flow resulting from low blood pressure, high intracranial pressure, or vascular occlusion of cerebral vessels; (*d*) local neuron activity—local increase in blood flow; (*e*) activity of cerebral vasoconstrictor (sympathetic) nerves; (*f*) activity of cerebral vasodilator (parasympathetic) nerves.

3. Passive changes in arterial caliber: mechanical responses to abrupt fluctuation in blood pressure.

In this report the author is concerned largely with the effect of the local neural vasomotor control and its application to the treatment of cerebral vascular occlusions. The interruption of the neural vasoconstrictor elements by procaine block of the cervical sympathetic chain is the basis of the treatment instituted to decrease the amount of permanent damage after such a clinical episode occurs.

Nosik outlines his technique for stellate-ganglion block. In his opinion, those patients who have had an embolic or a thrombotic cerebrovascular occlusion are more likely to derive benefit

from this procedure at little risk to themselves than are patients with a cerebral hemorrhage. The earlier the block can be performed, the better the possibility of forestalling associated anoxic changes in the neighboring cerebral tissue.

The use of stellate-ganglion block in treatment of cerebrovascular lesions does not alter the state of those neurons which are irreversibly damaged by anoxia, but, rather, is directed toward those cells included in the zone of vasospasm surrounding the affected area which are capable of being revived. By institution early of treatment with stellate block in patients with cerebrovascular occlusions, a close cooperation between the neurologist or neurosurgeon and the internist may result in greater decrease of neurological residua and in lessening of the degree of the patient's permanent disability.

ALPERS, Philadelphia.

MYASTHENIA GRAVIS: REPORT OF CASE RECEIVING UNUSUAL DOSAGE OF NEOSTIGMINE. J. A. RIDER, W. H. PICKETT, and A. W. HARRISON, Ann. Int. Med. **35**:463 (Aug.) 1951.

A patient with severe myasthenia gravis receiving 1,260 mg. of neostigmine bromide orally per 24 hours without toxic manifestations, but with poor response, was subjected to thymectomy. An acute myasthenic crisis developed 18 hours afer operation from lack of neostigmine due to gastric dilatation. The stormy, difficult postoperative course that resulted responded to heroic measures, including use of a respirator, tracheal intubation, aspiration, and bronchoscopy; neostigmine methylsulfate was given intramuscularly, reaching a dose of 336 mg. per 24 hours, a dose much greater than any previously recorded in the literature. The patient also received atropine sulfate, ephedrine sulfate, and tetraethylpyrophosphate, an anticholinesterase agent, and general supportive measures.

Tetraethylpyrophosphate appeared to be a valuable supplement to neostigmine in this case. Toxicity does occur, however. The authors point to the size of the pupil and its ability to react to light as a valuable sign of toxicity of neostigmine or tetraethylpyrophosphate. One of the first signs of toxicity can be a small pupil, which later becomes pinpoint, and finally dilated and fixed as toxicity progresses. As toxicity decreases, the pupil returns through the same stages in reverse order.

The effect of thymectomy in this case could not be considered striking. The patient has been maintained on a combination of tetraethylpyrophosphate and approximately one-fourth the preoperative dose of neostigmine bromide.

ALPERS, Philadelphia.

MESANTOIN IN EPILEPSY. N. A. BERCEL, B. FINESILVER, P. SOLOMON, E. SOMERFELD-ZISKIND, and E. ZISKIND, J. A. M. A. **143**:1460 (Aug. 26) 1950.

Eighty patients were treated with mesantoin® (methylphenylethylhydantoin) for two years. Of the total, 32 received mesantoin® alone, with an average dose of six 0.1 gm. tablets. The remaining 48 received other medication with it, the average dosage of mesantoin® for them being only four tablets. The daily dose of mesantoin® ranged from 0.1 to 1.3 gm.

Seizures of every type were reduced. Complete control occurred in the five patients with Jacksonian seizures. The reduction in monthly incidence of grand mal attacks was 77% greater than that with previous treatment. The total incidence of petit mal attacks per month was reduced 65%, the greatest effect being when there was admixture with grand mal. Psychomotor spells in combination with other types were reduced 62%, whereas the incidence of purely psychomotor spells acutally increased with administration of mesantoin.®

Better results were obtained in patients with more than one type of seizure whether mesantoin® was used alone or in combination with other drugs. In patients with petit mal seizures exclusively the addition of trimethadione (tridione®) enhanced the value of mesantoin.®

Comparison of statistics gathered after six months and after two years confirmed the constancy and reliability of the response of epileptic patients to mesantoin® therapy.

Bercel and his co-workers found that toxic effects may occur with mesantoin,® particularly when the drug is used beyond tolerance or when added to other heavy anticonvulsant medication. The most serious toxic effects were hematologic. More gradual administration will probably reduce toxic complications.

ALPERS, Philadelphia.

TUBERCULOUS MENINGITIS. H. CAIRNS, H. V. SMITH, and R. L. VOLLUM, J. A. M. A. **144**:92 (Sept. 9) 1950.

Recovery from tuberculous meningitis with the aid of chemotherapy is a slow process, requiring a year or more, as might be expected from the behavior of tuberculosis of other parts of the body. Streptomycin must be given to the patient for a long period, and treatment with the drug should be followed by rest and graduated exercise on sanatorium lines.

Cairns and his colleagues have treated 93 patients with tuberculous meningitis with streptomycin. For the first 60 of these patients the recovery rate was 50%. The majority of deaths occurred in the first three months; the relapse rate after a full course of treatment was low, 4 in 60. The authors have administered streptomycin for a much longer period than have most other workers in this field, and they hold the view that the course of the disease under treatment has justified their policy. As with tuberculosis in other parts of the body, in the meninges the inflammation is exceedingly slow to subside, even in the most favorable case; although at the end of six months of streptomycin therapy the cells and protein of the cerebrospinal fluid are usually approaching normal, it may take an additional 6 to 12 months before they are finally within normal limits, the protein level usually being the last to fall.

It is difficult to lay down precise rules for stopping treatment. The authors state that intrathecal injections should be continued daily for at least eight weeks after the last positive films or cultures, until cerebrospinal fluid studies show that the cell fluctuations have disappeared and the protein level is stationary or falling, until there is no clinical evidence of active disease, and, in particular, until the weight has ceased to diminish. Streptomycin intramuscularly administered should be continued for at least 180 days, regardless of the patient's progress. Its administration should not be stopped until the patient is gaining weight and the protein level and cell count of the cerebrospinal fluid have been steadily falling for at least two months.

All the authors' patients were treated in centers with facilities for minor neurosurgical operations. In spite of great care with the daily lumbar puncture, the spinal subarachnoid space became partly or completely blocked at some stage of the illness in about one-third of the patients. Bifrontal burr holes were immediately made, and the streptomycin was injected into the ventricles, or occasionally into the cisterna magna, until the lumbar subarachnoid space reopened. There should never be a day during treatment when the therapeutist does not have free access to the cerebrospinal pathways for giving streptomycin or for withdrawing cerebrospinal fluid to relieve increase of intracranial pressure.

Preliminary experiences with intrathecally injected tuberculin (purified protein derivative) have been encouraging from the therapeutic standpoint. The authors suggest these indicate that this substance results in a lysis of the exudate, and that in these circumstances streptomycin is a better remedy for tuberculous meningitis than has hitherto been supposed. Intrathecal use of tuberculin is being cautiously extended to a larger series of patients.

ALPERS, Philadelphia.

TREATMENT OF SPONTANEOUS SUBARACHNOID HEMORRHAGE. L. A. MOUNT, J. A. M. A. **146**:693 (June 23) 1951.

Spontaneous subarachnoid hemorrhage accounts for 2% of sudden deaths from natural causes. It is caused by the rupture of an intracranial aneurysm in the great majority of patients. It may occur at any age, but is commonest in the third, fourth, fifth, and sixth decades of life. It is characterized by the sudden onset of severe headache, stiffness of the neck, vomiting, collapse, and, in many instances, coma.

Mount feels that arteriography is essential to establishment of the diagnosis, both as to the location and as to the exact type of the pathologic process. Only then can definitive treatment be undertaken.

The mortality rate was 48% for the medically treated patients. This represents the average mortality rate in 752 cases, including several large series previously reported and the present series. The mortality rate was 14% for the surgically treated patients. This represents the average mortality rate in 469 cases, including the author's. The mortality rate in his own series was 11% for 77 consecutive patients with intracranial aneurysms treated by operation.

Mount concludes that it is therefore advisable in suspected cases of intracranial aneurysm to outline clearly the pathologic process by arteriography and to perform the surgical treatment indicated. While each case must be judged on its own merits, direct intracranial surgical treatment, when possible, is the best method.

ALPERS, Philadelphia.

SURGICAL TREATMENT OF LUMBAR DISK LESION, editorial, J. A. M. A. **146**:732 (June 23) 1951.

J. E. A. O'Connell (*J. Bone & Joint Surg.* **33-B**:8, 1951) analyzed the results of surgical treatment in 500 cases of proved lumbar-intervertebral-disk protrusion in which he operated. O'Connell infers from his experience that back pain from a protruded disk is seldom so severe, so persistent or so frequent as to require operation. Occasionally pain affected both lower limbs, either simultaneously or in succeeding attacks. In over 90% of cases it was felt in one leg alone, and the left was involved oftener than the right in the proportion of 3:1. A clinical diagnosis of lumbar-intervertebral-disk protrusion is more accurate than a myelographic diagnosis. O'Connell believes that neither lumbar puncture nor myelography is necessary for a diagnosis. The diagnosis is readily made in most cases by careful clinical and roentgenologic study. The problem is not in diagnosis, but in the decision as to the correct treatment.

Rest during the stage of acute symptoms, with later exercises for the lumbar muscles and joints, constitutes the correct treatment in most cases. Only when an adequate trial of such measures fails to bring relief should surgical intervention be considered. In most of the selected cases a carefully performed operation designed to relieve the affected nerve fibers from forces that stretch and compress them will give satisfying relief of symptoms. In O'Connell's series, 92% of the patients were either completely free from symptoms or greatly improved after operation.

In his discussion of the causes of unsatisfactory results from operative treatment of lumbar-disk lesions, J. R. Armstrong (*J. Bone & Joint Surg.* **33-B**:31, 1951) states that a wrong diagnosis is perhaps the most frequent cause of unsatisfactory surgical results. According to this author, the reason that the patient with a genuine disk lesion is not relieved by operation is failure to locate the lesion or failure to recognize a double lesion. He also states that it is not enough to remove the displaced nuclear tissue alone; the whole diseased nucleus must be removed.

Armstrong is opposed to the performance of arthrodesis in addition to removal of the herniated material. He believes that it is unecessary for the vast majority of patients and that it increases the immediate operative difficulties and hazards and greatly increases the period of postoperative incapacity. When necessary, arthrodesis can be performed in a second stage.

The views expressed by these British surgeons are very much in agreement with those of surgeons in this country.

ALPERS, Philadelphia.

ALCOHOL INJECTION INTO THE GASSERIAN GANGLION FOR RELIEF OF TRIGEMINAL NEURALGIA. R. ULLIK, Wien. klin. Wchnschr. **61**:450 (July 22) 1949.

Ullik describes an apparatus of his construction which permits the penetration of the injecting needle into the Gasserian ganglion with greater speed and accuracy. The author uses 96% alcohol for injection, approaches the ganglion along the axis of the trigeminal nerve, dispenses with x-ray control of the position of the needle, and follows the progress of the procedure by repeated neurological examinations during the operation. Light ether anesthesia for the introduction of the needle and the first few drops of the alcohol injection is used.

MASON, New York.

TREATMENT OF POST-ECLAMPTIC QUADRIPLEGIA WITH VITAMIN B_6 [PYRIDOXINE]. A. KRAUS, Wien. med. Wchnschr. **61**:492 (Aug. 5) 1949.

Kraus reports a case of postpartum eclampsia with quadriplegia, hemianopsia, motor aphasia, coma, and incontinence. Detoxifying and cardiotonic therapy maintained the patient alive. The neurological picture receded almost completely after 50 injections of a preparation of pyridoxine (vitamin B_6), given over a period of about three months.

MASON, New York.

Special Senses

AMYOTONIA CONGENITA: REPORT OF THREE CASES WITH REVIEW OF LITERATURE. J. A. EPSTEIN, J. Mt. Sinai Hosp. **16**:137, 1949.

Epstein reports three cases of amyotonia congenita in two male infants, aged 7 and 3 months respectively, and in one female infant, aged 21 months. All three patients presented the usual atonia, absence of reflex responses, and immobility. The clinical course and the necropsy findings indicate that there is a congenital deficiency of the entire motor apparatus, from the cells of Betz of the precentral convolution to the motor end-plates and striated muscle fibers of the effector mechanism. The essential pathologic features include a diminution in the number of pyramidal cells in the third and fifth layers of the precentral gyrus, including absence or pronounced reduction in number of the giant cells of Betz. The usual grouping of the neurons in the ventral horns is absent. There is a paucity of cells, persisting only as occasional small, stellate, deeply staining elements with few processes. Cells resembling neuroblasts are present in both the cortex and the nuclei of the medulla and pons. The ventral roots are deficient in medullated fibers as compared with the normal number of myelinated fibers in the dorsal roots. This discrepancy is further evidenced in the cauda equina. Motor end-plates are present only on the muscle fibers of normal size and have never been observed on the small embryonic fibers which form the outstanding pathologic feature of the voluntary muscles. The diaphragm is the only striated muscle to retain its normal appearance. These observations, together with the absence of evidence of degeneration, inflammation, or gliosis, suggest that amyotonia congenita is due to a failure of development and maturation of the voluntary motor components of the central nervous system before neurotization of the skeletal musculature has been established.

J. A. M. A.

Diagnostic Methods

CLINICAL AND EXPERIMENTAL STUDIES OF FLUORESCEIN DYES WITH SPECIAL REFERENCE TO THEIR USE FOR DIAGNOSIS OF CENTRAL NERVOUS SYSTEM TUMORS. G. E. MOORE, S. W. HUNTER and T. B. HUBBARD, Ann. Surg. **130**:637 (Oct.) 1949.

Moore and his associates direct attention to the use of sodium fluorescein in delineating malignant tissues. In earlier studies patients suspected of having an abdominal cancer, who were to undergo laparotomy, were given an intravenous injection of 1 gm. of the dye (20% aqueous solution) four hours before the scheduled exploration. Examination at the time of operation was carried out under the ultraviolet light emitted by a CH-4 mercury vapor lamp equipped with Wood's filter. The authors extended this fluorescein technique to tumors of the central nervous system and found that brain tumors almost invariably showed fluorescence when viewed with ultraviolet light. This technique has been of clinical value in the localization and diagnosis of subcortical lesions. Biopsy material is obtained by aspiration through brain needles. When examined under ultraviolet light neoplastic tissue fluoresces a bright yellow. Normal cortical material retains a faint yellow-green fluorescence, while normal white matter appears blue-white. The degree of fluorescence was correlated with the degree of malignancy. Acoustic neuromas and slow-growing astrocytomas took up the least amount of dye, whereas astroblastoma and glioblastomas appeared to fluoresce the most. Meningiomas differed; whereas some exhibited only slight fluorescence, others were a brilliant yellow. Tumors of the spinal cord were found to take up appreciable amounts of the dye. Residual remnants of tumor were occasionally disclosed by examination of residual cavity. A summary of 141 consecutive cases in which the fluorescein technique was used and in which a biopsy was done is presented. Efforts were made to tag fluorescein with radioactive elements. Radioactive diiodofluorescein containing 1 μc of I^{131} is injected intravenously. Some tumors, particularly those deeply situated, could not be localized with this radioactive method. Better equipment, more sensitive Geiger-Müller tubes, and other improved methods are required to increase the accuracy. The increased concentration of fluorescein dyes in brain tumors cannot be due to greater vascularity, since maximal fluorescence does not occur immediately after injection. The so-called blood-brain barrier undoubtedly is partly responsible for the differential concentration. Fluorescein and radioactive dyes may prove useful in evaluation of the role played by the blood-brain barrier in other diseases of the central nervous system.

J. A. M. A.

Encephalography, Ventriculography and Roentgenography

HYPERTROPHIC OSTEOARTHROPATHY: REPORT OF A CASE ASSOCIATED WITH A CHORDOMA OF THE BASE OF THE SKULL AND LYMPHANGITIC PULMONARY METASTASES. N. UHR and J. CHURG, Ann. Int. Med. **31**:681 (Oct.) 1949.

In the majority of cases, osteoarthropathy, with its concomitant clubbing of the fingers and toes, is seen as a sequel of chronic suppurative or neoplastic disease of the thoracic organs, and less commonly of the abdominal viscera. Only in rare instances has the condition been known to precede the manifestation of the underlying disease. When this occurs, diagnosis is often impossible until late in the course. The authors report an illustrative case, that of a white man aged 21 who showed early clubbing of the fingers and toes in the course of his rapidly progressive illness, which resulted in death in six months.

Autopsy confirmed the clinical impression of extensive neoplastic involvement of the lungs and massive hypertrophic arthropathy. The changes at the base of the skull were caused by a malignant tumor identical in structure with that found in the chest. The involvement of the lungs was of "lymphangiitic" variety, with only secondary infiltration of the parenchyma, bronchial walls, and blood vessels. There was no particular area which could have been designated as the primary focus. This fact argued against primary pulmonary neoplasm with metastases to the base of the skull. Reconsideration of the clinical course and detailed histologic studies led the authors to believe that the reverse, in fact, was true, namely, that the tumor originated within the base of the skull and metastasized to the lungs and pleura.

The microscopic structure strongly suggested the diagnosis of chordoma. The topography of the tumor, the location of the most differentiated areas beneath the sella turcica, and the expansion of the involved bones testified to the intraosseous origin of the growth.

Metastasizing chordomas of the base of the skull are not at all uncommon. However, even the malignant chordomas have a relatively slow course and may extend over a period of years. Cases such as that presented here, with rapid course and massive "lymphangiitic" metastases, must be rare.

Various theories have been propounded to explain the mechanism of osteoarthropathy and clubbing of fingers. It is apparent that none of the theories thus far suggested can adequately explain all cases.

ALPERS, Philadelphia.

CLINICAL STUDIES IN CRANIOSYNOSTOSIS: ANALYSIS OF FIFTY CASES AND DESCRIPTION OF METHOD OF SURGICAL TREATMENT. F. D. INGRAHAM, E. ALEXANDER JR., and D. D. MATSON, Surgery **24**:518 (Sept.) 1948.

Ingraham and his co-workers report 50 children with all varieties of premature closure of the cranial sutures for which the term "craniosynostosis" has been used. Twenty-nine children, 24 boys and 5 girls, presented premature closure of the sagittal suture. There were eight patients, five girls and three boys, with premature closure of the coronal suture, four patients with premature closure of the sagittal and coronal sutures, three with premature closure of the sagittal and lambdoid sutures, and six with closure of all cranial sutures. Twenty patients (40%), 7 of the sagittal group, 3 of the coronal group, and 10 with two or more sutures fused, were retarded to some extent before surgical treatment was practiced. Of the 44 patients treated surgically, 20 patients received treatment before the age of 1 year. Because of the rapid growth of the brain during the first year of life, it is to be expected that the best results from surgical treatment will be obtained during this period. This has been confirmed in the authors' cases. Many patients came to the hospital at ages varying from 3 to 7 years, and in these little was to be expected from any surgical procedure. In spite of this, there was definite improvement in the patients' behavior at home. Eleven patients (25%) showed retardation after operation. In general, the prognosis for mental development of a patient with premature closure of the cranial sutures treated under the age of 1 year is excellent, but if synostosis is evident at birth surgical therapy should not be delayed more than a few weeks. Linear craniectomy, with polyethylene film inserted over the bone edges to retard regeneration of bone, has been adopted as the operation of choice. There have been no operative deaths, wound infections, or serious complications.

J. A. M. A.

Congenital Anomalies

TIME OF OCCURRENCE OF COMPLICATION OF PREGNANCY AS CAUSAL FACTOR OF CONGENITAL ANOMALIES, B. GRÜNFELDER and W. LASCH, Ann. pædiat. **173**:388, 1949.

Grünfelder and Lasch cite observations which suggest that the predisposition to certain organic defects is determined by the affinity of cells which are of the same embryonal age, regardless of the later position in the body. In necropsies on monsters, they observed that in those with a defective rhinencephalon developmental anomalies were present also in the adrenals and in the genitalia. They deduced that if a noxious factor acts on the maternal organism at a time when the embryonic development of certain organs begins, the development of the first anlage is inhibited and this may lead to permanent anomalies in these organs. Experimental investigations on hen's eggs and rats were interrupted by war, but when the authors learned about the effects of rubeola in the mother during a certain stage of her pregnancy on congenital cataract and other anomalies in the offspring, they recalled the frequent concurrence of tumor of the pineal body and pubertas praecox or the occurrence of genital and adrenal symptoms in the presence of pineal tumors. They review data on 26 cases of this type. They believe that the reports from mothers of children with anomalies such as cardiac defects, cataract, harelip, and luxation of the hip joint, and the material they collected from the world literature support their view that the time when damage occurs during pregnancy is of much greater importance for the development of congenital anomalies than the nature of the damaging agent. It appears that rubeola produces the typical congenital malformations only if the infective or toxic agent affects the maternal organism during a specific time of pregnancy, i. e., when it occurs during the initial stage of the embryonic development of certain organs or organ systems.

J. A. M. A.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

James L. Poppen, M.D., Presiding
Regular Meeting, Oct. 11, 1951

Management in a Case of Electroshock Therapy Presenting Unusual Risk. Dr. W. McLaughlin, Dr. J. Wassersug, and Dr. J. Mackenzie.

A Negro woman, aged 20, was admitted to the Boston State Hospital on May 27, 1947, because she was said to be gradually withdrawing into herself, was melancholy, remained in her room all the time, and felt she was being criticized by others. During her period of observation she remained withdrawn, confused, and seclusive, but periodically became hyperactive and assaultive. She was silly, manneristic, and irrelevant. A diagnosis of dementia praecox, catatonic type, was made, and it was decided to give her electroshock treatment. However, the routine x-ray examination, in preparation for electroshock therapy, revealed that she had active pulmonary tuberculosis. A medical consultation was held with Dr. Hyman Morrison, who stated that although she had tuberculosis, her mental condition was such that electroshock therapy should not be withheld. He suggested a consultation with Dr. Wassersug, the tuberculosis consultant to the Boston State Hospital, who made the following report, on July 7:

"The patient appears to have a minimal active lesion in her right lung at the apex and the first intercostal space. Because of her age and race, I believe that the prognosis, even without the superimposed mental illness, is poor and that intensive therapy, such as pneumothorax, should be given promptly. I should like to have an examination of the sputum and another roentgenogram. After pneumothorax is established, shock therapy can be given."

Tubercle bacilli could not be identified in the sputum, and the patient's physical condition gradually grew worse because of her failure to eat and the development of catatonic excitement. On July 14 and 15 she was given her first pneumothorax treatments. These had to be carried out under intravenous thiopental anesthesia because of her acute excitement and disturbed condition. After a good collapse of the lung had been obtained with pneumothorax, she was given electroshock treatments, on an average of three times a week, with weekly maintenance pneumothorax therapy. After the fourth electric shock her mental condition was improved to the extent that she did not require thiopental for her pneumothorax treatments. She continued to show gradual improvement, and, after receiving 15 electroshock treatments, she was allowed to go out on trial visit on Oct. 12, four months after admission. She received maintenance pneumothorax therapy at a city public health unit, worked continuously as an office clerk, and was discharged from the hospital formally one year after the date of her release on visit.

We present this case as one in which combined psychiatric and medical management was a life-saving measure.

Eosinophile Response as a Clue to Prognosis in Insulin Treatment of Schizophrenia. Dr. H. C. Shands.

The progress of the eosinophile reaction in the course of insulin shock therapy was studied. The eosinophile counts were taken at random through the course of treatment, on the average at weekly intervals. Blood was drawn just before the termination of treatment on the given morning. Charts were presented to demonstrate that the occurrence of eosinophilia in these patients was associated with a poor prognosis, in that approximately 70% of patients with eosinophilia had a poor therapeutic result, while a similar proportion of patients without eosinophilia had good results in the immediate post-treatment period. Three patients from the series were presented to point out the difference in the two groups.

Remission in Schizophrenia Illness During Individual Psychotherapy, with Maintenance in the Community by Group Psychotherapy: Report of a Case. Dr. Jose N. Gurri.

A woman, aged 44, was admitted to the Boston State Hospital after a panic reaction, during which she suffered from frightening paranoid delusions.

At the age of 34 she had a catatonic episode, which lasted a few weeks. At 37 she spent eight months in a hospital, obtaining a good remission after insulin and electric shock treatments. On the present admission she was apathetic and disheveled; her mood was flat, and she had occasional unprovoked loud and abusive outbursts.

During psychotherapy her flat, bland mood was soon replaced by vehement expressions of feelings against the therapist, mingled with fear and distrust. This was followed by a strongly positive transference, with the intensity and tenacity of the schizophrenic who has at last found someone in whom he can completely and blindly deposit his trust. Her deep resentment was aired and violently acted out. When she left the hospital, her condition was in remission, and she had considerable insight. She went back to her job and is reported to be doing well.

Upon discharge she joined a psychotherapy group, in which she actively participates. She has been through several minor crises, which to her appeared of overwhelming importance, with that characteristic lack of knowledge for the most elemental aspects of interpersonal relationships found in the schizophrenic. A few clarifications have sufficed to solve these difficulties.

Psychotherapy in a Case of Schizophrenia. Dr. James Mann.

A woman, aged 29, with schizophrenia had had psychotherapy for four years. Her acute psychosis was resolved in 3½ months, and at the time of this report she had been maintaining herself independently in the community for 3½ years. In retrospect, she feels that the primary aid she received when acutely ill lay in the therapist's complete acceptance of her as he found her, not only in his refusal to withdraw in fear under the impact of her sexual demands, but also in his firm, but gentle, proscription of her activities with regard to him. For the first time in her life she felt that she was dealing with someone who was consistent and who created for her limits beyond which she could not go; thus, she felt that someone would exercise adequate control over her. After remission, the plan of treatment was threefold and included clarification of (*a*) the nature of her current activities and interpersonal relations outside the therapeutic situation, (*b*) feelings motivating her relationship to the therapist, and (*c*) the relation of *a* and *b* to sources found in her infantile experiences.

Treatment has clearly revealed the struggle between her wishes to destroy and her fear of similar retaliation. The sources of this struggle lay in intense deprivation at the hands of both parents, especially the mother. Her attempts at solution in her everyday relationships with people carried with them the wishes and fears already noted. Hence, all relationships were doomed to failure, as the object would withdraw in the face of her subtly hostile demands. Love meant for her the possibility of gratifying the desires never achieved in infancy. The infantile period was clothed in rage and fear; hence, adult love relationships were similarly invested. During treatment, a transference psychosis developed. By definition, it was acute and short-lived, a duplication of the setting that preceded her hospital admission, and clearly related to the transference situation. As the patient expressed it, "It all seemed familiar."

When the relationship of the psychotic patient to the therapist is a good one, the therapist should have more faith in that relationship than one usually sees. This means that rehospitalization at critical periods in therapy should be avoided, and can be avoided so long as the therapist makes himself available to the patient. The therapist becomes and remains a worth-while reality to the patient. Hasty hospitalization can render worthless that good reality, as the patient feels disappointment and failure in the eyes of the therapist.

CHICAGO NEUROLOGICAL SOCIETY

John Martin, M.D., President, in the Chair
Regular Meeting, Oct. 9, 1951

Sensory Changes with Herniated Nucleus Pulposus. Dr. Loyal Davis, Dr. John Martin, and Dr. Stanton L. Goldstein.

We have made a careful study of the sensory changes in 500 consecutive cases of surgically verified herniated nucleus pulposus. In all but 38 cases myelography was performed and the lesion verified. Of the 500 cases, sensory changes, which were extremely variable, were demon-

strated in 327. Herniations at the fourth-fifth lumbar interspace alone produced 38 patterns of sensory involvement. No typical sensory pattern could be demonstrated for herniations at this interspace. Herniations at the fifth lumbar-first sacral interspace produced 29 sensory patterns, none of which was typical. Herniations at these two levels could not be differentiated on the basis of sensory changes alone. The extreme variability in the sensory pattern makes the method of devising a dermatome chart on the basis of the sensory changes associated with herniated nucleus pulposus an unreliable one. While myelography is not necessary to establish the diagnosis of herniated nucleus pulposus, we believe it is necessary to localize a lesion involving the lumbar portion of the spine.

DISCUSSION

DR. BENJAMIN BOSHES: The problem posed by the authors is an old one, and one as yet unsolved. One may start with the literature of the middle 30's, when surgery for herniated disk became established, and one will find every kind of regimen for diagnosis. At one end of the scale stands the group which demands careful clinical review, examination of the spinal fluid for increased protein, and x-ray evidence, either direct or with a contrast medium—iodized oil or air. At the other end, formerly, stood Walter Dandy, who "required," in his own words, only a good history, with evidence of radicular involvement, and the patient was ready for surgery. He recommended exposure of the vertical spines, permitting tests for increased mobility of the suspected vertebra. The affected disk would lie under the area of greatest movement.

The argument still goes on. Is Foerster right in his statement that there is no critical sensory loss when a single posterior root is cut? Is Keegan, with his large number of carefully studied cases of solitary-root lesions, a more careful examiner than Foerster? Is scratch better than pinprick as a testing modality? Are touch and temperature stimuli better than pinprick (Spurling and Grantham)? The New Zealand investigators, under Falconer, say that all others are wrong in part. Involvement of a single dermatome due to involvement of a single root may be complicated by what these investigators call "spreading hypalgesia or hyperalgesia." The findings depend on whether there is much associated pain or paralysis.

My own experiences are in keeping with those of the Falconer group. There is nothing more difficult than a careful sensory examination. This requires standardized stimuli; a quiet, warm room, and, most of all, a reasonably intelligent, cooperative patient. A man who has been bedridden for weeks with a painful thigh is not going to be too particular as to whether a given stimulus is less or greater than a preceding one. Weakness and paralysis are often interpreted as "numbness." Sensation from such a limb is often "rejected." "My leg feels dead," is the answer given by the patient.

To make disk surgery reasonably foolproof, one must use every possible diagnostic aid to clarify the issue. There are many recorded cures, so called, of the disk syndrome by psychotherapy. Such patients are poor subjects for surgery.

The technique described by Drs. Davis, Martin, and Goldstein tries to avoid these pitfalls, and they establish a good rationale for their diagnostic regimen. I have seen, and often participated in, the work-up of their cases. A careful history, neurological examination, and x-ray study lead to the diagnosis of a herniated disk. The sensory alterations are painstakingly documented on the chart, modality by modality. Then the ethyl iodophenylundecylate (pantopaque®) study follows. The dye usually outlines the affected anatomical level even if the sensory findings are variable. The history and neurological examination will catch the rare "concealed" disks which do not show on examination with the contrast medium. The patients I have seen thus examined have not been disturbed by the procedure, and the effective removal of the contrast medium eliminates any potential aftermath of nerve-tissue reaction.

In my opinion, until sensory examinations are standardized and dermatomes universally agreed upon, the method described by the authors will give the highest percentage of accurate anatomical localizations of the disk. It follows that the site of any subsequent operation will be better defined and the procedure less traumatic to the patient.

DR. I. JOSHUA SPEIGEL: I am in full agreement with the authors in everything that has been said, particularly with regard to the great variability of sensory changes to be found with rupture of an intervertebral disk involving the fourth and fifth lumbar and first sacral nerve roots. I am surprised, however, to hear that the authors have not encountered difficulties with

ethyl iodophenylundecylate myelography similar to those my colleagues and I have encountered in our clinic. Forty-two of 150 consecutive myelograms performed at the Michael Reese Hospital and elsewhere were followed either by severe headache, lasting for days, or an elevation of temperature to as high as 104 F., lasting for two or three days, or both. As in all other clinics, an attempt is made to remove the pantopaque® in its entirety, if possible. A culture was made of the contrast medium, and, of course, no growth was obtained. We were assured by the company that the chemical composition of the pantopaque® was the same in all cases. I saw in consultation two patients on whom a pantopaque® myelogram had been obtained elsewhere, followed by complete paraplegia. Neither of the myelographic studies was performed by a neurologist or a neurosurgeon. I have seen so many cases in which there was myelographic, but not surgical, evidence of ruptured disk, and, conversely, so many cases in which the myelograms gave no evidence of the lesion but in which a free-lying ruptured intervertebral disk was removed surgically that I am coming to believe that, unless there is a specific reason for contrast myelography, it would be wiser to explore the interspace between the fourth and the fifth lumbar vertebra and that between the fifth lumbar and the first sacral vertebra without carrying out myelography.

Dr. R. P. Mackay: Any careful clinical neurologist will readily testify that the sensory examination is by far the most difficult part of the neurological study. The findings presented by the authors of this paper confirm this judgment. To see on the screen, as we have, practically the whole lower extremity colored red as indicating the sensory changes supposed to result from a lesion of a single root simply means that the patient has deluded himself, has misunderstood the test, or has deceived the examiner. The technique of the sensory examination must make the test scrupulously objective, and this can be done only by having the patient respond to each single stimulus. Repetitive or scratch stimuli are confusing to the patient, and to the physician, even in the normal subject, because of the irregular distribution of pain spots and because of the suggestion implied in the question, "Tell me when it gets dull," or even in the question, "Tell me whether it changes."

I am in entire agreement with the authors' conclusion that the sensory examination is of little or no value in the diagnosis of herniated disk. The sensory diagnosis, on the other hand, must be reached by careful analysis of data concerned with the mode of onset; the character and distribution of the pain; its response to exercise, movement, coughing, or sneezing; the presence or absence of local tenderness, motor weakness, or pain on straight-leg raising, and the state of the deep reflexes. With data on these points, the diagnosis may usually be made without much help from the sensory examination, or even from the myelogram.

Dr. Frederick Hiller: The discussion of this interesting paper reminds me of another "variable," which has not been mentioned. Obviously, it is not only the intelligence of the examiner, and not only the failure of the patient, which interferes with the accurate determination of the pattern and outline of the sensory disturbances. It is also the variation in the distribution of the sensory disturbances which occurs during observation. I can tell you from my own subjective experience that paresthesias—and also hypesthesias—vary from day to day, under the influence of a varying impingement on the posterior root fibers. Thus, the pain may be felt at times in certain portions of the thigh or the leg or in the foot. This variability of sensory manifestations may well contribute to the contradictory or unreliable "objective" findings in the examination of sensation.

I should be interested to hear some comments on the important differential diagnosis of the disk syndrome and the syndrome of root compression seen in chronic arthritis of the spine.

Dr. John Martin: I should like to add that these myelograms were often made even when we realized that it was not absolutely necessary. The greater number of these patients were examined at a Veterans Administration hospital, where one can have a certain amount of clinical investigation done. The sensory findings and the plain roentgenograms of the spine do not localize a lesion accurately, and these two criteria may indicate in the same patient the possibility of a lesion being at different levels. Myelography was performed in 100% of the cases in this group. I thoroughly agree that the less that is put into the subarachnoidal space the better, and that includes air, as well as ethyl iodophenylundecylate (pantopaque®).

DR. STANTON L. GOLDSTEIN: In answer to your questions, Dr. Hiller, I do not think it would be possible to go into the differential diagnosis of low-back pain and sciatica at this time. This paper was limited to a discussion of the sensory changes with herniated nucleus pulposus.

We realize the importance of the physical examination, history, neurological examination, and all the other diagnostic aids. However, even when all these are taken into account, we have found that our preoperative localization was wrong in a great number of cases. While it is true that if we were to explore both the fourth and the fifth interspaces routinely we should probably find a large proportion of the herniations, we feel that we can make a more accurate preoperative diagnosis with the aid of myelography and thus reduce the time and morbidity rate of the operation. All this, though, is beside the point of this paper, which is simply that we have found that the sensory changes are not consistent or accurate enough to localize the lesion, as many have contended.

We have not encountered any of the complications that Dr. Speigel mentioned. There have not been any elevations of temperature, certainly none as high as he has stated. We have had no paraplegias resulting from myelography. It is true that occasionally, when there are good signs and symptoms of a herniated nucleus pulposus, we have operated in the absence of myelographic evidence. However, there have not been many of these instances.

A Technique for Teaching Testing for Aphasia. DR. JOE R. BROWN, Minneapolis.

For the purpose of instructing fellows in medical specialties how to test for aphasia, a simple test was constructed. Many of the test items were selected from a much more complex test for aphasia previously reported.

The test consists of a series of 30 cards. Each card includes appropriate directions, in addition to test material. Pictures are used instead of actual objects because of convenience and because they have almost the same meaning in our culture. Various language components are sampled individually by the test materials on each card. These components include auditory recognition, auditory association, auditory comprehension, visual association, visual comprehension, calculation, word finding, spoken expression, spoken formulation, written expression, and written formulation. When indicated by the responses to these test cards, additional cards dealing specifically with apraxia and visual agnosia are used.

(Twelve illustrative cases were reviewed briefly.)

DISCUSSION

DR. R. P. MACKAY: I wish to compliment Dr. Brown on his lucid presentation of an ingenious scheme. Of course, the scheme is based upon the concept of a cortical mosaic of functions or capacities. We are all aware of the deficiencies of such a concept, but it still makes a great difference in the symptoms whether a lesion is located in one part of the brain or in another. I am always disturbed when I examine a patient with aphasia because the loss of a simple ability would seem to require the loss of a complicated ability. If a man cannot handle a brick, how can he build a house? If a patient has inability to manage simple language functions, which inability would suggest a lesion in one area, how can he perform more complicated language functions, the loss of which would suggest a lesion in another area? Perhaps Dr. Brown can help me in this dilemma.

DR. HERMAN CHOR: How long does it take to give this test—all in one sitting?

DR. R. P. MACKAY: How quickly do the uninitiated learn to give this test?

DR. PERCIVAL BAILEY: Are these cards available to other clinicians?

DR. JOE R. BROWN, Minneapolis: Much of the credit for the test material belongs to Dr. Hildred Schuell, who worked with the much more complex test for aphasia which we reported previously.

One question concerned the necessity for precautions against lip reading. Everyone utilizes visual cues in interpreting language. When material as simple as that in this test is used, the aphasic patient may be able to recognize by visual cues (lip reading) the difference, for example, between the spoken word "pencil" and the spoken word "key." The precaution against lip reading would seem unnecessary if complex test material were being used.

The rest of the questions and comments deal with localization of lesions with theories of neural function as they relate to language.

The major emphasis of my talk was directed toward a description of a test for aphasia. The case material used for illustrative purposes naturally arouses interest in localization of lesions producing various types of aphasia and in the various theories of language mechanisms. Obviously, the material I presented does not offer any answers to these problems. In constructing the test itself, I have tried to sample various language components separately, without feeling that it was necessary to postulate a specific anatomical location for a function in order to test it individually. By analogy, we test the pain of a pinprick and light-touch sensibility of an area of the skin individually without assuming that they are necessarily represented in different areas in the brain.

The various parts of the test, once it was constructed, were then related to the localization of lesions as described by Nielsen. At this point, it seems appropriate to note that many years ago Hughlings Jackson emphasized that there was a great difference between the location of a lesion which destroyed a function and the conclusion that the function itself was necessarily performed in the same area. I believe that it is important to test aphasic patients specifically, to apply the best available information to localizing the lesion, and to add to our sum of knowledge on aphasia. It seems that a lesion placed anteriorly destroys the ability to express language, that a lesion in the temporal lobe impairs auditory components of language, and that a parieto-occipital lesion impairs visual components. Language formulation may be impaired by a lesion of the temporo-occipital junction or its projections forward.

In answer to Dr. Chor's question: The test is given in one sitting and takes 15 to 30 minutes.

In answer to Dr. Mackay: After giving the test two or three times, the resident has gained a fairly good idea of the fundamentals of aphasia and knows what is going wrong with a particular patient's speech.

When results of the test are being evaluated, it is important to consider the massing of errors. It is true that a severe defect in one language component may produce some impairment of other components.

John Martin, M.D., President, in the Chair
Regular Meeting, Nov. 13, 1951

Treatment of Temporal Arteritis with Cortisone. Dr. Sidney Schulman and Dr. Delbert Bergenstal.

The generally accepted method of treatment of temporal arteritis has been surgical resection of the involved portions of the superficial temporal arteries. This procedure usually results in striking relief of the local pain and tenderness but does not affect the general symptoms or the course of the disease, and does not provide prophylaxis against the frequent and severe ocular complications from involvement of the retinal arteries. A variety of medical therapeutic approaches have been found ineffective. Recently, however, two cases in which cortisone appeared to have induced a rapid cure have been reported (Schick, R. M.; Baggenstoss, A. H.; Fuller, B. F., and Polley, H. F.: *Proc. Staff Meet., Mayo Clin.* **25**:492, 1950). The authors have observed a similar result in a third case. In all three cases symptoms had been present for only slightly more than a month before treatment was begun. This represents a total duration of illness which is significantly shorter than the average of seven months in the natural course of the disease. No relapses were noted in any of the three cases during follow-up periods of approximately three months each after treatment was discontinued. Attention is also directed to a recent report of two cases of temporal arteritis in which aureomycin appeared to have a beneficial effect (Rice-Oxley, J. M., and Cook, A. M.: *Lancet* 1:2, 1951.

DISCUSSION

Dr. B. Bishes: I wonder whether Dr. Schulman or his associates, in their review of the literature, came across any instance in which the vessels of the brain stem were involved in this disease. I recall a case of temporal arteritis which had progressed to total blindness in which brain-stem symptoms typical of thrombosis of the posterior inferior cerebellar artery

developed. Unfortunately, the patient was taken home, and she died about six months later. Permission for autopsy could not be obtained. I wonder whether the authors have any opinion in regard to this.

DR. R. P. MACKAY: May I ask whether there is any connection between temporal arteritis and polyarteritis (periarteritis) nodosa? The pathologic description of temporal arteritis is reminiscent of the changes in polyarteritis nodosa. Since the latter disease is said to respond rather well to cortisone and corticotropin, the connection between the two might be intimate.

DR. SIDNEY SCHULMAN: In answer to Dr. Boshes' question: We found no reports in the literature of pathologically verified involvement of cerebral vessels, other than the retinal arteries, in cases of temporal arteritis.

In answer to Dr. Mackay's question: It is true that some have considered temporal arteritis and polyarteritis nodosa as variants of the same disease, and it is said that in some instances the histologic appearance of temporal arteries in patients with temporal arteritis is indistinguishable from that of affected arteries in polyarteritis nodosa. Generally, however, I believe that the two can be histologically distinguished. Further, the distribution in the vascular system is quite different, polyarteritis nodosa affecting small and medium-sized arteries, with emphasis on the visceral vascular bed, and temporal arteritis affecting the temporal arteries, the aorta, and some of the larger branches of the aorta, such as the common iliac and the subclavian arteries. Finally, when one considers certain clinical features of the two diseases, particularly the fact that polyarteritis nodosa is a uniformly fatal disease and affects chiefly young men, and temporal arteritis is self-limited and affects predominantly elderly women, the conclusion is inescapable, in the present state of knowledge, that temporal arteritis and polyarteritis nodosa are basically different.

I am not aware that the occurrence of eosinophilia in temporal arteritis has been reported.

Relation of the Hypothalamus to Bulbar Poliomyelitis: A Clinicopathologic Study.
DR. A. B. BAKER, Minneapolis.

In 115 cases of bulbar poliomyelitis the hypothalamus was studied at three levels, namely, (1) the level of the mamillary bodies, (2) the level of the tuber cinereum, and (3) the level of the optic chiasm. The nuclei which were selected for study consisted of the supraoptic, the paraventricular, and the tuberal, in the anterior portion; the dorsomedial, the ventromedial, and the lateral, in the middle portion, and the posterior and the mamillary, in the posterior portion of the hypothalamus. Inflammatory changes were present in 85% of the cases, while at least 5% or more cell damage within one or more of the nuclear groups was shown in 61%. During the acute illness many of these patients revealed clinical evidence of hypothalamic dysfunction. Thirty patients manifested hyperthermia; 4 hypothermia; 10, severe persistent hypertension, and 16, gastrointestinal symptoms. Twelve patients who apparently had made a complete recovery from their bulbar poliomyelitis were subjected to a battery of tests of hypothalamic function. Six of these patients showed abnormal responses to these special tests.

It is apparent from these studies that the hypothalamus is commonly involved in bulbar poliomyelitis. A patient with a partially damaged hypothalamus may be quite capable of sustaining existence in the protected environment of the hospital. However, under the stress situations of the normal environment he may acquire a large number of physical complaints, many of which may even jeopardize life. It would appear that a careful evaluation of hypothalamic function in poliomyelitis is of equal importance with the determination of the extent and degree of muscular paralysis and will greatly aid the physician in properly advising his patient on discharge from the hospital.

DISCUSSION

DR. OSCAR SUGAR: In the sections of the hypothalamus there was, I noted, considerable involvement of the subthalamic nucleus of Luys. Have you ever noted any sort of involuntary movements associated with bulbar poliomyelitis?

DR. J. A. LUHAN: About a year ago, in the course of sectioning a formalin-fixed brain from a case of bulbar poliomyelitis, I was struck by the appearance of extreme hyperemia, and even petechial hemorrhages, in the hypothalamus only. On reviewing the history of this case, I noted that the first symptoms of the illness were those of inordinate appetite (bulimia) and

thirst, probably as a result of the severe involvement of the hypothalamus. Incidentally, in the same brain I found two symmetrical holes, the result of necrotic inflammatory softening, in the center of the reticular formation of the medulla oblongata, one on each side of the midline. Dr. Baker had already described such focal necrosis in his cases several years ago. My own experience in studying the histopathologic appearance in cases of poliomyelitis in Cook County Hospital for the past 11 years leads me to believe that some change in the propensity for necrotic change has occurred in the poliomyelitis virus, revealed by the appearance only within the last two years or so of such an acute necrotizing inflammatory reaction. I wonder whether Dr. Baker has observed any such transformation over the course of years in the histopathologic characterization of epidemic poliomyelitis.

DR. H. LADWIG: I should like to ask Dr. Baker whether involvement of the bladder function is thought to be primarily mechanical in origin.

DR. HAROLD LAWN: In the cases of hypothalamic involvement did the white blood cell count and the red blood cell count show any change?

DR. RICHARD RICHTER: I should like to add a random observation to Dr. Baker's systematic collection of data implicating the hypothalamus in the symptomatology of poliomyelitis. During a small local outbreak of the disease a year ago, a patient with the ordinary acute spinal poliomyelitis was admitted to my service on the third day of her paralysis, which was confined to the lower extremities. At no time did signs of bulbar paralysis or any degree of respiratory paralysis develop, and she never appeared to be anoxic. On the fourth day of her paralysis, which was also the last day of fever, she rather abruptly became subject to fits of excitement and panic and, at the same time, frequently dozed for short periods. There was also vasomotor collapse; her blood pressure fell to 80/60, and her pulse was rapid, and at times almost imperceptible. During the same period there was excessive thirst, and for four days the daily urinary output was between 5,000 and 6,000 cc. This is probably not a unique observation, but it is the only instance of diabetes insipidus caused by poliomyelitis of which I am aware.

DR. A. B. BAKER, Minneapolis: My colleagues and I are now carrying out a detailed clinical study of all our cases of bulbar poliomyelitis in order to evaluate the significance of the various hypothalamic disturbances. At present we have completed our gastrointestinal studies. From an attempt to correlate the nuclear changes in the hypothalamus with the severe gastrointestinal disturbances of these patients, it would appear that certain nuclear groups might well be more severely involved than others. The tuberal nucleus showed three times as much destruction as was seen in other cases of bulbar poliomyelitis, while the paraventricular nucleus showed twice as much involvement. This localization corresponds fairly well with that described in the literature in experimental animals.

I agree with Dr. Luhan that from 1946-1950 the virus of poliomyelitis has apparently been more virulent, producing in many cases an inflammatory necrosis of the nervous system. Prior to this time I do not recall having seen such severe inflammatory changes in this disease. Actually, however, the important pathologic process is the one that involves the nerve cells. The inflammatory necrosis is striking histologically, but is important clinically only because of the extent to which it implicates the neurons.

I do not know why patients with bulbar poliomyelitis have bladder disturbances. From our studies so far, we have not arrived at an answer to this question.

None of our patients with hyperthermia secondary to hypothalamic disturbances showed changes in the white blood cell count, which in most cases remains within normal limits.

I believe Dr. Richter's comments are important. For some time we have questioned the occurrence of a purely spinal type of poliomyelitis. Clinically, the patient may appear to have involvement only of the spinal cord, but one wonders whether pathologically the entire nervous system may not be affected, with the spinal cord showing the predominant implication. Certainly, many patients with clinical involvement of the spinal cord alone probably have widespread damage to the nervous system, which could well account for the symptoms manifested by Dr. Richter's patient.

Cryptococcosis (Torulosis): Clinical and Experimental Studies. DR. WILLIAM H. MOSBERG JR.

With the help of lantern slides, the following studies were discussed:

1. Subcultures of Cryptococcus neoformans isolated from the central nervous system of 30 patients with cryptococcosis were collected. The behavior of this group of organisms was then studied on 26 sets of carbohydrate media (Mosberg, W. H., Jr., and McAlpine, J. D.: Torulosis of the Central Nervous System: Biochemical Behavior of the Causative Organism, *Bull. School Med. Univ. Maryland* **36**:122-125 [July] 1951.

2. It was found possible to produce cryptococcosis of the central nervous system by intracranial inoculation in mice, guinea pigs, rabbits, cats, and dogs. Only the mouse could be consistently infected (Smith, G. W.; Mosberg, W. H., Jr.; Manganiello, L. O. J., and Alvarez de Choudens, J. A., to be published).

3. Since there are apparently differences in virulence among different strains of C. neoformans, a method of offering a prognosis as to life expectancy is desirable. The length of survival of a mouse after intracranial injection of a given subculture is roughly proportional to the length of survival of the human patient from whom that organism was cultured. J. S. Wagner and G. W. Smith (unpublished experiments) believe that this mouse virulency test may be used as a method of offering a prognosis as to life expectancy in cases of human cryptococcosis.

4. The pH appears to be a factor in the growth of C. neoformans. Patients have been treated with large doses of alkalinizing substances (Mosberg, W. H., Jr., and Arnold, J. G., Jr.: *Ann. Int. Med.* **32**:1153-1183 [June] 1950. Mosberg, W. H., and Alvarez de Choudens, J. A.: *Lancet* **1**:1259-1260 [June 9] 1951).

5. Laboratory studies suggest that alkalinization and fever might be advantageously combined in the treatment of human cryptococcosis (Mosberg, W. H., and Alvarez de Choudens, J. A.: *Lancet* **1**:1259-1260 [June 9] 1951).

PHILADELPHIA PSYCHIATRIC SOCIETY

Hugo Mellar, M.D., President, in the Chair
Regular Meeting, Oct. 4, 1951

Vocational Rehabilitation in a Neuropsychiatric Hospital. JOHN C. PHILLIPS, Coatesville, Pa.

The vocational rehabilitation of a neuropsychiatric patient leaving the hospital is of primary importance to his over-all adjustment. The vocational rehabilitation unit of the Veterans Administration Hospital at Coatesville is charged with the task of bringing about favorable vocational conditions for the patient, so that he may have a maximum chance to make a good adjustment in society.

The patient undergoes a thorough program of testing—intelligence, interest, achievement, and special aptitude tests are administered. Information on personality factors is obtained from the psychiatrist and the clinical psychology service. These test results are considered in the light of the general medical, psychiatric, social, educational, and vocational histories. A determination is made as to the vocational areas in which the patient is best fitted to work, and a thorough discussion of these with members of the hospital team narrows the field to a few suitable occupations. The patient takes part in interviews with the vocational counselor, who interprets the results of the testing program and discusses with him possible courses of future action. Group-guidance meetings offer occupational information and motivate the patient.

As a matter of preparing the way for acceptance of patients with a neuropsychiatric history, vocational conferences are held for business men and labor leaders of communities served by the hospital. A full one-day program acquaints them with the rehabilitation possibilities of the patient.

Two cases were cited. Patient A, hospitalized 13 years, carried the diagnosis of dementia praecox, paranoid type. He had no significant vocational background. Eleven months after

leaving the hospital, he has earned a promotion in a painter's job. Patient B, hospitalized numerous times over four years, carried the diagnosis of traumatic encephalopathy and chronic alcoholism, and had had an enucleation of the right eyeball. He was placed in a work-adjustment program, and then was given a position as stock clerk in a chain food store. He has earned a promotion.

Electroshock as an Adjunct to Nutritional Therapy: Presentation of Film.

Nutritional difficulties frequently arise in resistive patients with long-term psychoses, despite availability of adequate diet and personal care. Occasionally, some of these patients become progressively emaciated to a point that malignant disease is suspected. In the author's experience, electroshock followed by total-push therapy has proved a valuable means of reestablishing ideal weights, with concomitant psychiatric improvement. The progress of two such patients from an emaciated state to nutritional balance was portrayed in the film.

Functioning of the Psychological Service at Veterans Administration Hospital, Coatesville, Pa. DR. MARGARET MERCER, Coatesville, Pa.

Since competent clinical psychologists are scarce and all psychological services are likely to be understaffed, it is necessary to decide what are the most important contributions the service can make to the total hospital program.

The work of the clinical psychology service at Coatesville may be described under the three main headings: testing, teaching, and research.

At present, the research projects are limited to a type designed to answer definite and immediate questions. Larger staffs may be free to work on projects of long-range value, but we cannot at present, in justice to immediate needs of patients.

Since this institution is a teaching hospital, teaching responsibilities are heavy. A course in mental hygiene has been developed for affiliate nurses, and there is a weekly psychology seminar for residents. The seminar is designed to help the resident use psychological reports effectively and to acquaint him with psychological research, which is also of interest to psychiatrists and neurologists. The hospital carries on a psychiatric orientation program for undergraduate medical students, to which the psychological service is giving an increasing amount of time. The work with these students is planned to give the student a brief introduction to the dynamics of intellectual functioning and the impact of psychosis upon it, as well as elementary consideration of personality dynamics as reflected in projective tests. The students take some tests themselves if they wish and have conferences on the psychological examinations of the patients assigned to them for intensive study.

Over one-half the time of the psychological service is spent in testing. If a testing service is to make a genuine contribution to the study of patients, the psychologist must take responsibility for making clear its structure and function to the other professional services.

It has been our experience in this situation that we learn very rapidly to work together. The speed and enthusiasm with which residents learn to make really intelligent use of psychological service make clinical psychology in a neuropsychiatric hospital a very satisfying job.

News and Comment

ANNUAL CHARLES A. ELSBERG LECTURE

Dr. Gilbert Horrax, neurosurgeon to the Lahey Clinic, to the New England Deaconess Hospital, and to the New England Baptist Hospital, Boston, will deliver the annual Charles A. Elsberg Lecture, established by the New York Society of Neurosurgery, on Tuesday, March 18, 1952, at the New York Academy of Medicine, 2 East 103 St., New York, at 8:30 p. m. Dr. Horrax has chosen for his subject "The Development of Brain Tumor Surgery."

APPOINTEES TO EDITORIAL BOARD OF *NEUROPSIQUIATRIA*

The following persons have been appointed to the editorial board of *Neuropsiquiatria*, published in Buenos Aires: W. Bruetsch; W. Freeman; P. Hoch; M. Moore; T. Putnam; R. Wartenberg.

Book Reviews

Health and Human Relations in Germany. Report of the Second Conference on Problems of Health and Human Relations in Germany, Williamsburg, Va., December, 1950. Pp. 30. Josiah Macy Jr. Foundation, 565 Park Ave., New York 21, 1951.

An opportunity to carry further the work of the Princeton conference came when several Germans attended the White House Conference on Children and Youth. A meeting was arranged at Williamsburg, with Dr. John R. Rees again serving as chairman. At this conference there were, as before, American, English, and French participants, but more Germans. The German members pointed out that the statements about German character (pages 49-54 of the report of the first conference) were somewhat questionable; so the following statement was prepared and unanimously adopted:

"The Williamsburg conference is of the opinion that the attempt to explain historically and psychologically the nature and origin of the German character, as outlined in the report of the Princeton conference on pages 49 to 54, is affected by the historical period in which it was written and is a somewhat one-sided post-war document. This attempt is not wholly just. The explanation as given does not consider sufficiently Germany's particular geographical position, the specific features of the development and structure of German economy, with their special social and cultural effects. The Williamsburg conference believes that the attitudes expressed in the Princeton report on pages 92 to 121 contain a more adequate understanding of the present-day German situation.

"The Williamsburg conference believes that very careful cooperative efforts of historians, psychologists, and sociologists, working closely together, will be needed in order to arrive at a more reliable picture of the German character.

"The Williamsburg conference desires most sincerely to make a contribution to prevent prejudices and to create a spirit of genuine, constructive cooperation based on sincere mutual understanding."

The rest of the conference was largely taken up in discussing one by one each of the thirteen special recommendations made at the Princeton conference.

Frontal Lobotomy and Affective Behavior: A Neurophysiological Analysis. By John F. Fulton. Price, $3. Pp. 160, with illustrations. W. W. Norton & Company, Inc., 101 Fifth Ave., New York 3, 1951.

This small volume represents the Salmon Lectures for 1950. Fulton was slow to see the implications of his work with Jacobsen on the relation of frontal lobotomy in the chimpanzee to the use of frontal lobotomy on man for the relief of mental disorders and pain. In fact, it

was ten years before he organized a research program at Yale to bring about an understanding of the neurophysiologic alterations that go along with the psychologic alterations after lobotomy and similar procedures. Now he is making up for lost time, and in this monograph he is able to refer to a large number of studies under way at Yale and elsewhere, the results of which will probably be published in due course.

Fulton is a neurophysiologist, and the material at his disposal is so vast that he cannot do justice to it all. There are so many perplexing, confusing, and contradictory results that his power of analysis tends to break down when he compresses the results into such small compass. The result is that he comes up with some shrewd guesses that may or may not prove to be the correct ones. For instance, he champions a modification of lobotomy used by Grantham on a handful of patients (whom Grantham reported as 22 patients subjected to 35 operations for the relief of unbearable pain). Fulton may, indeed, be correct in pointing to the inferior medial quadrants of the frontal lobes as of major importance in the relief of pain. However, he is really sticking his neck out when he recommends resection of the cingulate area in disturbed schizophrenic patients, and his designation of the "orbito-temporo-cingulo-amygdaloid region" as a proper field of operations for the relief of slowed-up, inhibited patients covers a great deal of territory, to say the least. Fortunately, the connections of one part of the brain with another, as revealed by physiologic neuronography and other methods, attract his major interest, and in this respect the monograph is a useful one in collating the advances in this particular field.

Electroencephalography in Clinical Practice. By Robert S. Schwab, M.D. Price, $6.50. Pp. 195, 106 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1951.

With the remarkable pioneering of the Cambridge and St. Louis schools of neurophysiology, most of the mystery of the working mechanism of single axons was unraveled and reduced to the level of simplicity and reliability of a mathematical equation. Berger's introduction, in 1929, of a method of observation applied to the baffling complexity of neuronal aggregates, was, at the same time, fascinating and discouraging. The fact that the science of electroencephalography received immediate clinical application, before the fundamental nature of brain waves was investigated, that, in other words, the pioneer electroencephalographer of two score years ago was deluged with a multitude of practical inquiries before the ink was dry on the first record ever taken, gives us only the measure of avidity for knowledge of those to whom this book is dedicated: neurologists, internists, pediatricians, psychiatrists, and neurosurgeons. Electroencephalography grew up in our time, and members of the medical profession assumed toward it a wide range of positions, with blind faith and ultraconservative incredulity at the extremes, depending on individual attitudes toward scientific insecurity. Something new in medicine was also added to this confusion, namely, the uncomfortable feeling of not quite understanding the seemingly "way-over-my-head" language of the electroencephalographer, which a practicing physician often considered supramedical, but which physicists often derided as being infratechnical. Now comes this book, written in simple, conversational style, with the badge of common sense affixed to every chapter head. The author has written with a laudable sense of perspective and proportion, without rationalization when dealing with imponderables and without patronization when tackling a seeming certainty. He has even written with humor. A fellow electroencephalographer finds few points with which to argue; if some signs of dogmatism are noted (e. g., "the normal sleep record is of course bilaterally symmetrical"), he may write them off as inevitable in a book that admittedly tries to be simple—as long as it is not misleading. This book is a "must" for those interested in electroencephalography. Any future complaint that there is not enough interdisciplinary understanding, or that—we heard it often—electroencephalographers hide their uncertainties in their own semantic smoke screen, will no longer be fair and, even less, justified.

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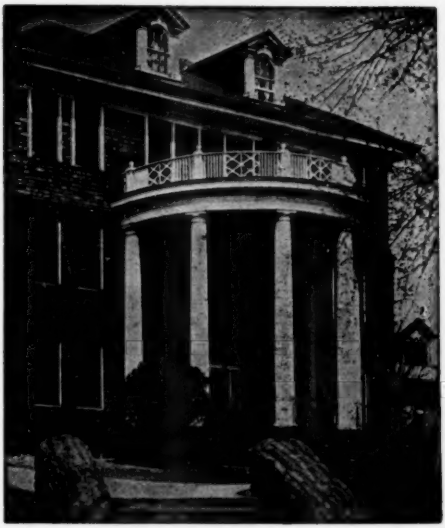

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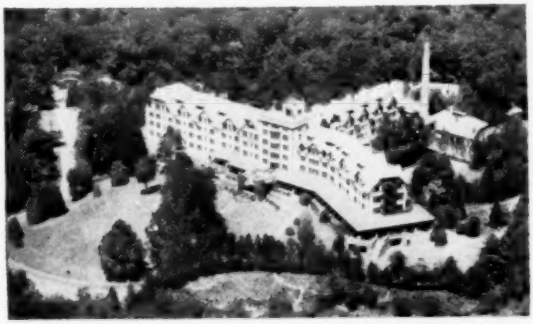

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